

FORM PTO-1390 (Modified)  
(REV 11-98)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

5882-66-BD

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/980540

INTERNATIONAL APPLICATION NO.  
PCT/FR00/01174

INTERNATIONAL FILING DATE  
28 April 2000

PRIORITY DATE CLAIMED  
28 April 1999

TITLE OF INVENTION

1-AMINO TRIAZOLO[4,3-A]QUINAZOLINE-5-ONES AND/OR -5-THIONES INHIBITING  
PHOSPHODIESTERASE IV

APPLICANT(S) FOR DO/EO/US

GAUDILLIERE, Bernard; LAVELETTE, Remi; ANDRIANJARA, Charles; BREUZARD, Francine

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
  - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
- ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
- ☒ A copy of the International Search Report (PCT/ISA/210).
- ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
  - a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☐ have not been made and will not be made.
- ☒ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
- ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
- ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
- ☒ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☐ Other items or information:

Express Mail No. EF378128419US

U.S. APPLICATION NO. (IF KNOWN) <b>09/980540</b>	INTERNATIONAL APPLICATION NO. <b>PCT/FR00/01174</b>	ATTORNEY'S DOCKET NUMBER <b>5882-66-BD</b>
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21. The following fees are submitted:				<b>CALCULATIONS PTO USE ONLY</b>	
<b>BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5)) :</b>					
<input checked="" type="checkbox"/>	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO .....		<b>\$970.00</b>		
<input type="checkbox"/>	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO .....		<b>\$840.00</b>		
<input type="checkbox"/>	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO .....		<b>\$690.00</b>		
<input type="checkbox"/>	International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) .....		<b>\$670.00</b>		
<input type="checkbox"/>	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) .....		<b>\$96.00</b>		
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				<b>\$970.00</b>	
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				<b>\$0.00</b>	
<b>CLAIMS</b>	<b>NUMBER FILED</b>	<b>NUMBER EXTRA</b>	<b>RATE</b>		
Total claims	39 - 20 =	19	x \$18.00	<b>\$342.00</b>	
Independent claims	2 - 3 =	0	x \$84.00	<b>\$0.00</b>	
Multiple Dependent Claims (check if applicable). <input checked="" type="checkbox"/>				<b>\$280.00</b>	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				<b>\$1,592.00</b>	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable). <input type="checkbox"/>				<b>\$0.00</b>	
<b>SUBTOTAL =</b>				<b>\$1,592.00</b>	
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).				<b>\$0.00</b>	
<b>TOTAL NATIONAL FEE =</b>				<b>\$1,592.00</b>	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). <input type="checkbox"/>				<b>\$0.00</b>	
<b>TOTAL FEES ENCLOSED =</b>				<b>\$1,592.00</b>	
				<b>Amount to be refunded</b>	\$
				<b>charged</b>	\$

- ☐ A check in the amount of \_\_\_\_\_ to cover the above fees is enclosed.
- ☒ Please charge my Deposit Account No. **23-0455** in the amount of **\$1,592.00** to cover the above fees.  
A duplicate copy of this sheet is enclosed.
- ☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **23-0455** A duplicate copy of this sheet is enclosed.

**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

Claude F. Purchase, Jr.

NAME

47,871

REGISTRATION NUMBER

25 October 2001

DATE

**Novel 1-Amino Triazolo [4,3-a] Quinazoline-5-ones and/or -5-thiones inhibitors of Phosphodiesterases IV**

**Field of the invention**

5 The present invention relates to novel triazolo [4,3-a] quinazoline-5-ones and/or -5-thiones useful for drug preparation for treatment by therapy with a phosphodiesterases 4 inhibitor. These drugs are useful in particular as anti-inflammatories, anti-allergics, bronchodilators, anti-asthmatics, or  $\text{TNF}\alpha$ . inhibitors.

10 **Background of the invention**

The cyclic adenosine 3', 5'-monophosphate (AMPC) is an second ubiquitous intracellular messenger, acting as an intermediate between a first messenger (hormone, neurotransmitter, or autacoid) and the cellular functional responses: the first messenger stimulates enzyme responsible of the AMPC synthesis; AMPC intervenes then, relying of the cells implicated, in very numerous functions: metabolic, contractile, or secretory.

The effects of AMPC terminate when it is broken down by cyclic nucleotide phosphodiesterases, intracellular enzymes that catalyze its hydrolysis into inactive adenosine 5'-monophosphate.

In mammals we distinguish at least seven large families of cyclic nucleotide phosphodiesterases (PDE) numbered from 1 to 7 according to their structure, their kinetic behavior, their substrate specificity, or their sensitivity towards effectors (Beavo J.A. et al (1990) Trends Pharmacol. Sci. 11, 150-155. Beavo J.A. et al (1994) Molecular Pharmacol. 46, 399-405). PDE4s are specific to AMPC.

Some phosphodiesterase non-specific inhibitors are known as inhibiting several families of enzymes. This is the case for some methylxanthins like theophyllin. These compounds have a weak therapeutic index, in particular because of their action on some classes of PDE present in cells other than target cells. Additionally, some families of PDE may be selectively inhibited by various pharmacological agents : hydrolysis of cyclic nucleotides slowed down and therefore their concentration increase in only cells the type of PDE sensitive to the inhibitor is found.

Of interest are the phosphodiesterases 4 (PDE4), which have been identified in numerous tissues including the central nervous system, heart, vascular endothelium, vascular smooth muscle and the one of air passage muscle, myeloid and lymphoid lines.

AMPc increase in cells implicated in inflammation inhibits their activation : inhibition of synthesis and mediator release in mastocytes, monocytes, eosinophil and basophil polynuclears, inhibition of chemotactism and degranulation of eosinophil and neutrophil polynuclears, inhibition of division and differentiation of lymphocytes.

- 5 The cytokins, in particular TNF and interleukins, produced by different leukocyte classes such as T lymphocytes and eosinophil polynuclears, play an important role in the triggering of inflammatory manifestations in particular in response to stimulation by an allergen in respiratory tracts.

Further, AMPc decreases air passage smooth muscular fiber tonicity; PDE4 inhibitors bring  
10 about bronchorelaxation.

Chronic obstructive pneumopathy (chronic obstructive pulmonary disease or COPD) is a chronic pathology, of slow evolution, characterized by obstruction of respiratory tracts (associated with inflammation of respiratory tracts and elevated neutrophil count). Pulmonary function alteration is largely irreversible (although improvement is possible after treatment by  
15 bronchodilators).

Clinical presentation of chronic obstructive pneumopathy may fluctuate according to attack severity, going from simple non-invalidating chronic bronchitis to very invalidating conditions like chronic respiratory insufficiencies. The main clinical characteristics of patients suffering from chronic obstructive pneumopathy are chronic bronchitis and/or emphysema  
20 (associated with respiratory tract inflammation and/or elevated neutrophil count).

Over the last years, some selective inhibitors of second-generation phosphodiesterase 4 have been suggested as potentially efficient agents in treatment of chronic obstructive pneumopathy. See, among others, Doherty, *Chemical Biology* 1999, 3:466-473 ; Mohammed and al, *Anti-inflammatory & Immunodilatory Investigational Drugs* 1999 1(1) :1-28 ; Schmidt  
25 and al, *Clinical and Experimental Allergy*, 29, supplement 2, 99-109.

Ariflo that is a PDE 4 inhibitor active by oral route, has been suggested for chronic obstructive pneumopathy treatment. See, among others : Nieman and al, *Am J Respir Crit Care Med* 1998, 157 :A413 ; Underwood and al, *Eur Respir J* 1998, 12 :86s ; Compton and al, *Am J Respir Crit Care Med* 1999, 159 :A522. See also the oral presentation by Compton  
30 during the meeting of the "European Respiratory Society" which was held in Madrid, on 12<sup>th</sup> October 1999, as well as the one by Torphy and Underwood during the 4<sup>th</sup> worldwide congress on inflammation which was held in Paris, from 27<sup>th</sup> to 30<sup>th</sup> June 1999. Ariflo is currently under study, in some phase III clinical trials, for chronic obstructive pneumopathy treatment.

However, we should point out that Ariflo has some drawbacks. Indeed some significant adverse events, of the nausea and vomiting type, have been reported after administering of a dose of 20 mg as a single intake. See Murdoch and al, Am J Respir Crit Care Med 1998, 157 :A409. Appearance of adverse effects at such low doses will limit the call for Ariflo and prevent use of daily single dosage pharmaceutical, leading therefore to patient discomfort.

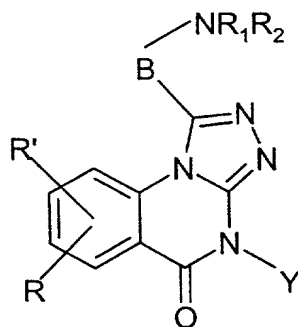
Osteoporosis is a disease characterized by bone mass decrease and skeleton architecture loss, leading to bone fracture. A large number of women, at the post-menopausal stage, suffer this disease and patient numbers keeps increasing.

Two types of distinct cells exist in bone : osteoblasts, which participate in bone formation ; and osteoclasts, which play a role in bone resorption. More particularly, bone mass results from the sum of bone formation by osteoblasts and bone resorption by osteoclasts. Consequently, molecules inhibiting bone resorption induced by osteoclasts are efficient in osteoporosis treatment. Calcitonin, biphosphonates and possibly estrogens are agents fighting against resorption and they are used in the clinical area. Molecules stimulating bone formation by osteoblasts also constitute some promising agents in osteoporosis treatment. See also, Yoshihiro et al Jpn. J. Pharmacolog. 1999, 79, 477 – 483.

For several years, extensive research has been performed to obtain and develop powerful PDE4 inhibitors. This has proved to be difficult due to the fact that lots of potential PDE4 inhibitors have some activity on phosphodiesterases in other families.

To date, the lack of selectivity of PDE4 inhibitors represents then an important problem, given the extent of functions regulated by AMPc. There is now a need for powerful and selective PDE4 inhibitors, thus without effect on PDE belonging to other families.

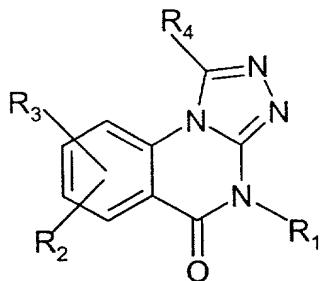
European patent EP 0076199 disclosed compounds with the following general formula :



in which R and R', identical or different, represent H, halogen, alkyl C<sub>1-3</sub>, alkoxy or nitro ; Y represents alkyl cycloalkyl C<sub>3-8</sub>, alkenyl C<sub>2-4</sub>, aryl ou aralkyl group, and B represents (CH<sub>2</sub>)<sub>n</sub> with n = 1, 2, 3 or CH(CH<sub>3</sub>). The use of these compounds is suggested for treatment of asthma, bronchitis and allergic disorders.

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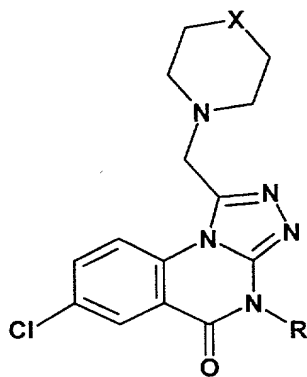
Patent DDR158549 disclosed compounds with the following general formula :



in which R<sub>1</sub> represents H, alkyl or aryl ; R<sub>2</sub> and R<sub>3</sub> represent H, alkyl, halogen, OH, SH, O-alkyl, S-alkyl ; R<sub>4</sub> represents H, alkyl, halogenoalkyl, OH, SH, O-alkyl, S-alkyl, SO<sub>2</sub>-alkyl, NH<sub>2</sub>, SCN, aryl, (CH<sub>2</sub>)<sub>n</sub>COOalkyl and n = 0 to 2. The use of these compounds is suggested as diuretics and antianaphylactics.

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Ram and al., in J.Prakt.Chem, 1990, 332(5), 629-39 describe compounds with the following general formula :



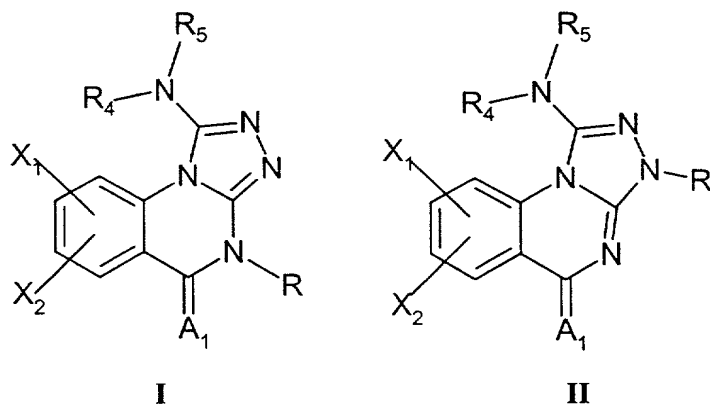
(X) R=CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>  
X= C, NH, N-CH<sub>3</sub>, N-Ar

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The use of these compounds is suggested for treatment of high blood pressure.

## Summary of the invention

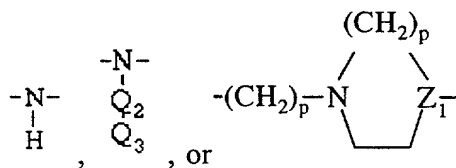
The invention related to triazolo [4,3-a] quinazoline-5-ones and/or -5-thiones of formula I or II :



I and II are position isomers of group R on nitrogens 3 or 4, in which :

- A<sub>1</sub> is O or S ;
- X<sub>1</sub> and X<sub>2</sub>, similar or different, represent :
- hydrogen, hydroxy, halogen, amino, nitro, mercapto, cyano, carboxy,
- lower alkyl, lower alkoxy or -S(O)<sub>m</sub>R<sub>8</sub> in which m is 0, 1 or 2 and R<sub>8</sub> is a lower alkyl, possibly substituted by one or several halogen atoms,
- -CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub> in which :

-Q<sub>1</sub>- is : a simple valence bond, -O-,

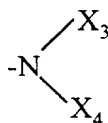


and Z<sub>1</sub> is CH, N, O or S,

-Q<sub>2</sub>- is :

- a) -(CH<sub>2</sub>)<sub>q</sub>-, q being equal to 0, 1, 2, 3, or 4, or
- b) -(CH<sub>2</sub>-CH<sub>2</sub>-O)<sub>r</sub>-, r being equal to 2, 3, or 4, and

-Q<sub>3</sub> is : -H, -OH, lower alkoxy, -O-CO- X<sub>3</sub> -NHX<sub>3</sub> or



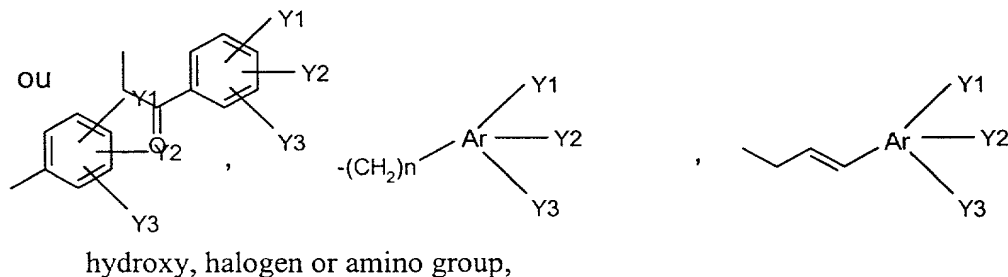
in which  $X_3$  and  $X_4$ , similar or different, represent one group  
lower alkyl,  $X_3$  and  $X_4$  could be bound to form a cycle, including one or several heteroatoms  
chosen amongst O, S or N,

-  $-NH-R_1$  in which  $R_1$  represents a lower alkyl group, possibly substituted by one or several  
groups chosen amongst halogen, hydroxy, cyano, lower alkoxy or  $-CO-Q_1-Q_2-$   
 $Q_3$ , or

-  $-NR_2R_3$  in which  $R_2$  and  $R_3$ , similar or different, represent a lower alkyl, possibly  
substituted by one or several hydroxy, halogen, cyano, lower alkoxy or  $-CO-Q_1-Q_2-Q_3$   
groups,  $R_2$  and  $R_3$  being able to be linked to form a cycle, including one or several  
heteroatoms chosen amongst O, S or N and possibly bridged by a lower alkyl, gem  
dialkylated or substituted by one or several groups chosen amongst hydroxy, keto,  
lower alkyl, alkoxy or  $-CO-Q_1-Q_2-Q_3$ ;

- R represents :

- lower alkyl, lower alkenyl, lower alkynyl, aryl alkynyl, 2, 3 or 4 pyridylalkyl  
possibly substituted by a lower alkyl, a lower alkoxy, a



in which :

- $n$  is an integer between 1 and 5,
- Ar is an aromatic cycle including 5 or 6 atoms with 0 to 3 heteroatoms chosen among O, S or N.
- $Y_1$ ,  $Y_2$  and  $Y_3$ , similar or different represent :
  - hydrogen, hydroxy, mercapto, amino, nitro, halogen,  $-NHR_1$ ,  $-NHR_2R_3$ , -  
 $(CH_2)_s-CN$ ,  $-(CH_2)_s-CO-Q_1-Q_2-Q_3$  in which  $s$  is an integer between 0 to 6 ;
  - lower alkyl, lower alkoxy or  $-S(O)_mR_8$  in which  $m$  is 0, 1 or 2 and  $R_8$  is a lower alkyl, each one may be possibly substituted by one or several halogen atoms ; and



- R<sub>4</sub> and R<sub>5</sub>, represent :

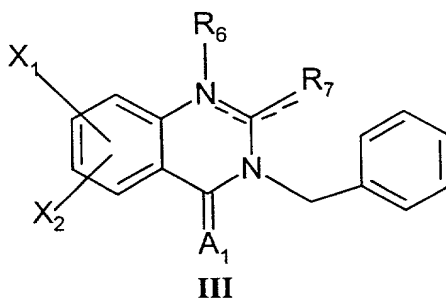
- lower alkyl when R<sub>4</sub> and R<sub>5</sub> are similar, aralkyl, cycloalkyl or cycloalkyl alkyl, when R<sub>4</sub> and R<sub>5</sub> are different,
- lower alkyl, R<sub>4</sub> and R<sub>5</sub> being able to be linked to form a saturated cycle or including one or several double-bonds including one or several heteroatoms chosen among O, S or N and possibly substituted by lower alkyl, hydroxy or lower alkoxy or bridged by a lower alkyl, gem dialkylated or substituted by one or several groups chosen from hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>, two atoms of a cycle then formed may also be part of another cycle chosen among phenyl or heteroaryl comprising from 4 to 8 atoms with 1 to 4 heteroatoms ;

possibly their racemic forms and their isomers, as well as their pharmaceutically acceptable salts.

Compounds of the present invention are useful as inhibitors, particularly as selective inhibitors of phosphodiesterase enzyme, and more particularly the PDE4 enzyme.

The invention relates also to compounds mainly used as synthesis intermediaries of a formula I or II compounds.

A first series of intermediaries includes compounds having the following general formula III :  
in which :

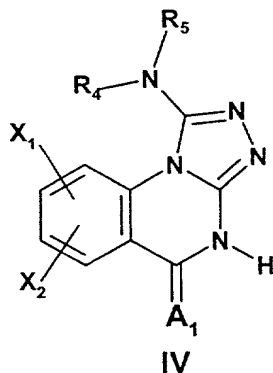


- X<sub>1</sub>, X<sub>2</sub> and A<sub>1</sub> are such as defined previously ;
- the dotted lines represent optional double-bonds ;
- R<sub>6</sub> is hydrogen ; and
- R<sub>7</sub> is S or hydrazino ;

R<sub>7</sub> being able to be linked to nitrogen on R<sub>6</sub> to form a cycle, particularly a triazole, possibly substituted by a lower thioalkyl, mercapto or halogen group.

A second series of intermediaries includes compounds having the following general formula

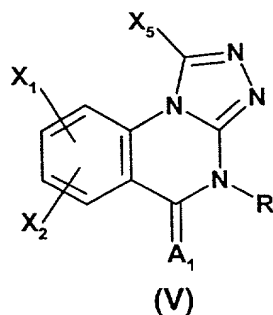
5 IV:



in which X<sub>1</sub>, X<sub>2</sub>, A<sub>1</sub>, R<sub>4</sub> and R<sub>5</sub> are such as previously defined.

A third series of intermediaries includes compounds having the following general formula V:

10 :

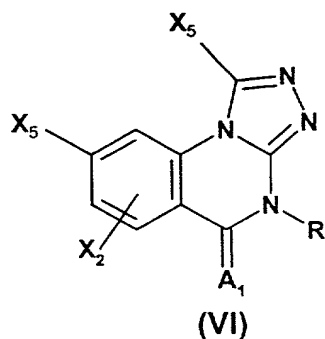


in which X<sub>1</sub>, X<sub>2</sub>, A<sub>1</sub> and R are such as previously defined and X<sub>5</sub> is a halogen group, particularly F, Br or Cl, -OCOX<sub>7</sub>, -OSO<sub>2</sub>X<sub>7</sub> or -SO<sub>2</sub>X<sub>7</sub> in which X<sub>7</sub> is a lower alkyl or an aryl group .

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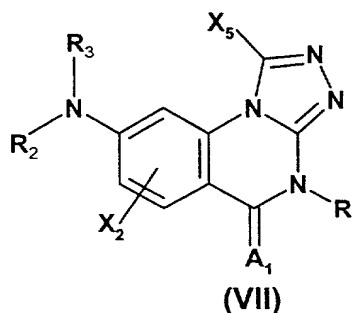
A fourth series of intermediaries include compounds having the following general formula VI

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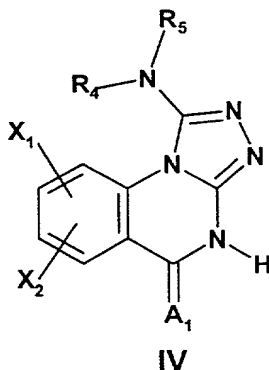
in which  $X_2$ ,  $X_5$ ,  $A_1$  and R are such as previously defined.

A fifth series of intermediaries include compounds having the following general formula VII :



in which  $X_2$ ,  $A_1$ ,  $R_2$  and  $R_3$  are such as previously defined,  $X_5$  is a halogen group, particularly F, Br or Cl,  $-OCOX_7$ ,  $-OSO_2X_7$  or  $-SO_2X_7$  in which  $X_7$  is a lower alkyl or an aryl group .

The invention relates also to a process for producing formula I and II compounds. The process is characterized as including the reaction of general formula IV compounds:



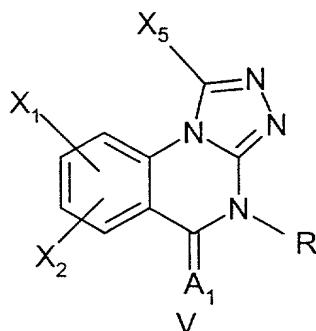
in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are such as previously defined,  
with a general formula compound



in which R is such as previously defined and  $X'$  is a halogen group, particularly F, Br or Cl,  $-OCOX_7$  or  $-OSO_2X_7$  in which  $X_7$  is a lower alkyl or aryl group ;

to obtain a mixture of general formula I and II compounds which are then possibly separated.

General formula I compounds can be also prepared by a process characterized in that it includes reacting general formula V compounds:



in which  $X_1$ ,  $X_2$ ,  $A_1$  and  $R$  are such as previously defined and  $X_5$  is a halogen group, particularly F, Br or Cl,  $-OCOX_7$ ,  $-OSO_2X_7$  or  $-SO_2X_7$  in which  $X_7$  is a lower alkyl or an aryl group ;

with a general formula compound :

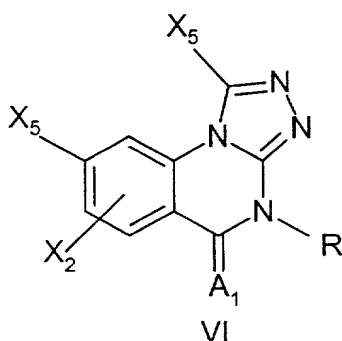


in which  $R_4$  and  $R_5$  are such as previously defined,

to obtain a general formula I compound.

In particular manner, when  $X_1$  is  $-NR_2R_3$  and  $-NR_2R_3$  and  $-NR_4R_5$  are identical, general formula I compounds adhering to this definition can be obtained by reacting with a general

formula VI compound :



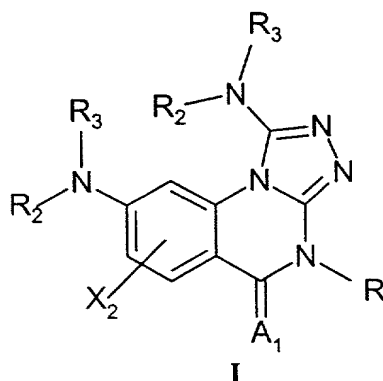
in which  $X_2$ ,  $X_5$ ,  $A_1$  and  $R$  are such as previously defined,

with a general formula compound :



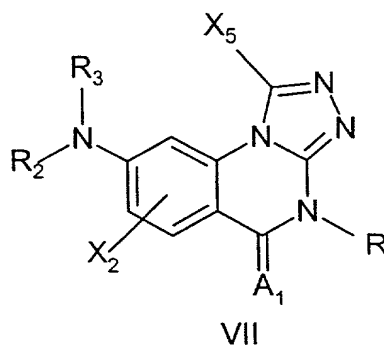
in which  $R_2$  and  $R_3$  are such as previously defined,

to obtain a general formula I compound :



Also in particular manner, when  $X_1$  is  $-NR_2R_3$  and  $-NR_2R_3$  and  $-NR_4R_5$  are different, general formula I compounds adhering to this definition can be obtained by reacting with a general

5 formula VII compound :

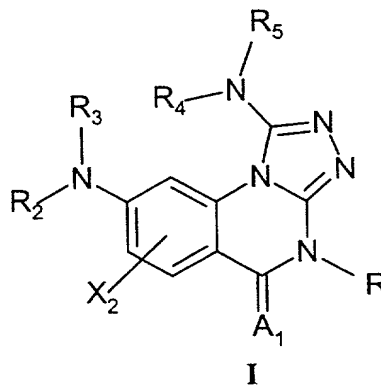


in which  $X_2$ ,  $X_5$ ,  $A_1$ ,  $R$ ,  $R_2$  and  $R_3$  are such as previously defined,  
with a general formula compound :



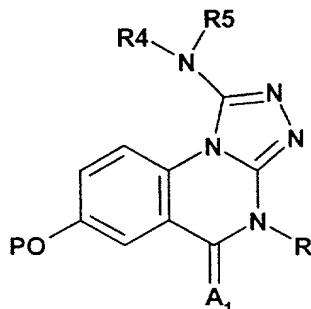
in which  $R_4$  and  $R_5$  are such as previously defined,

10 to obtain a general formula I compound :



Also in particular manner, when  $X_1$  is H and  $X_2$  is OH, general formula I compounds adhering to this definition can be obtained by subjecting a general formula Ia<sub>1</sub> compound :

in which  $A_1$ , R,  $R_4$  and  $R_5$  are such as previously defined and P is a protector group,

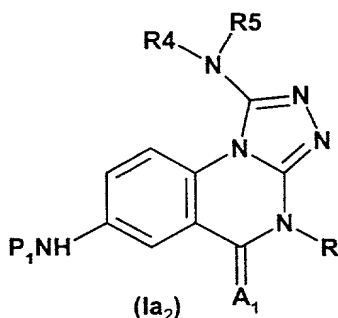


(Ia<sub>1</sub>)

to conditions allowing protector group P elimination to obtain a general formula I compound.

Also in particular manner, when  $X_1$  is H and  $X_2$  is NH<sub>2</sub>, formula I compounds adhering to this definition can be obtained by subjecting a general formula Ia<sub>2</sub> compound

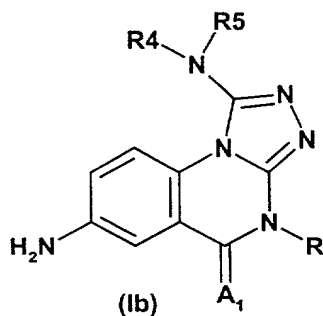
in which  $A_1$ , R,  $R_4$  and  $R_5$  are such as previously defined and P<sub>1</sub> is protector group,



(Ia<sub>2</sub>)

to conditions allowing elimination of the protector group P<sub>1</sub> to obtain a general formula I compound.

Also in particular manner, when  $X_1$  is H and  $X_2$  is NHR<sub>2</sub> in which R<sub>2</sub> is such as previously defined formula I compounds adhering to this definition can be obtained by reacting with a general formula Ib compound



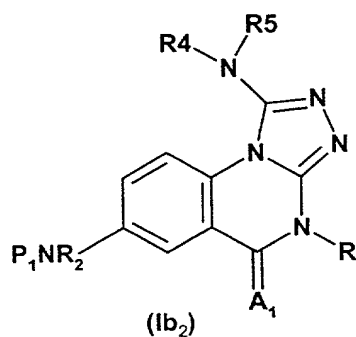
(Ib)

in which  $A_1$ , R,  $R_4$  and  $R_5$  are such as previously defined,

- 5 with a formula  $R_2X_5$  compound in which  $R_2$  and  $X_5$  are such as previously defined, to obtain a general formula I compound.

Moreover, when  $X_1$  is H and  $X_2$  is  $NHR_2$  in which  $R_2$  is such as previously defined, formula I compounds adhering to this definition can be also obtained by subjecting a general formula

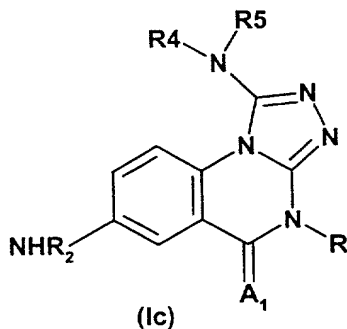
- 10  $Ib_2$  compound :



in which  $A_1$ , R,  $R_4$  and  $R_5$  are such as previously defined and  $P_1$  is a protector group, to conditions allowing protector group elimination, to obtain a general formula I compound.

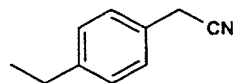
- 15 Also in particular manner, when  $X_1$  is H and  $X_2$  is  $NR_2R_x$  in which  $R_2$  is such as previously defined and  $R_x$ , represents  $R_2$  or  $R_3$  as previously defined, formula I compounds adhering to this definition can be obtained by reacting with a general formula Ic compound :

in which  $A_1$ , R,  $R_2$ ,  $R_4$  and  $R_5$  are such as previously described,



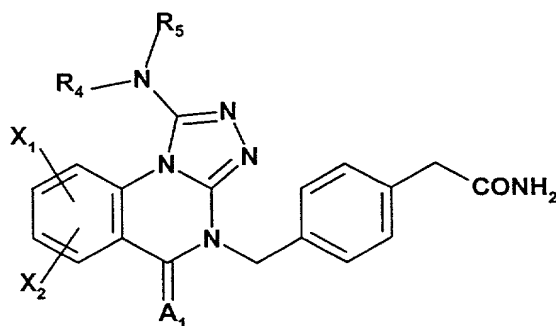
with a formula  $R_xX_5$  compound in which  $R_x$  and  $X_5$  are such as previously defined, to obtain a general formula I compound.

Also in particular manner, when R is



5

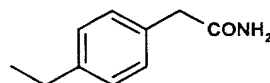
formula I compounds adhering to this definition can be obtained by dehydration of a general formula Ig compound:



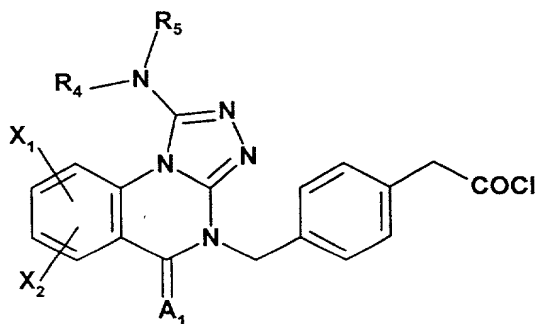
(Ig)

in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are such as previously defined, to obtain a general formula I compound.

Also in particular manner, when R is



15 formula I compounds adhering to this definition can be obtained by reacting with a general formula If compound :

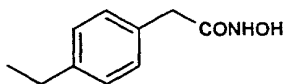


(If)



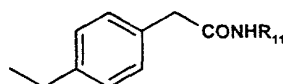
in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are such as previously defined,  
with ammonia to obtain a general formula I compound.

Also in particular manner, when R is



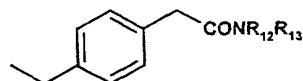
formula I compounds adhering to this definition can be obtained by reacting with a general  
formula If compound with hydroxylamin to obtain a general formula I compound.

Also in particular manner, when R is



formula I compounds adhering to this definition can be obtained by reacting with a general  
formula If compound with a formula  $R_{11}NH_2$  compound in which  $R_{11}$  has the same  
significance than  $R_2$ , to obtain a general formula I compound.

Also in particular manner, when R is



formula I compounds adhering to this definition can be obtained by reacting with a general  
formula If compound with a formula  $HNR_{12}R_{13}$  compound in which  $R_{12}$  and  $R_{13}$  have the  
same significance than  $R_4$  and  $R_5$  respectively, to obtain general formula I compound.

The invention relates also to a pharmaceutical composition including a formula I or II  
compound and a pharmacologically acceptable carrier.

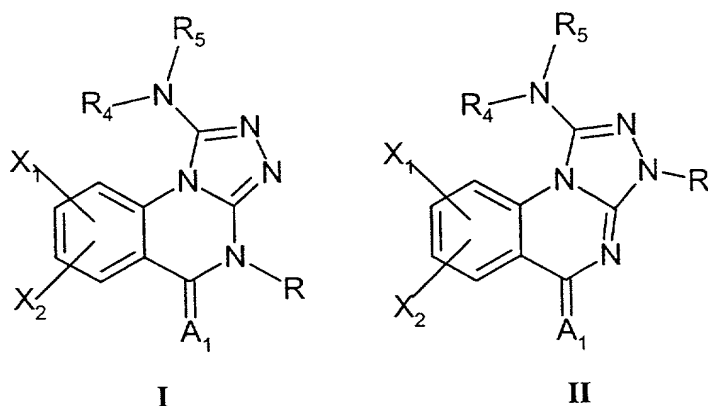
The invention relates also to the use of a formula I or II compound for drug preparation in  
treatment disease or illness relying on therapy by phosphodiesterase inhibition, and more  
particularly of PDE4.

The invention relates also to a treatment method relying on therapy by phosphodiesterase inhibition, and more particularly of PDE4, said method including administering an effective concentration of a formula I or II compound to a patient.

5

### Detailed description of the invention

The current invention relates also to general formula I or II compounds :



in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R$ ,  $R_4$  and  $R_5$  are such as previously defined.

10

The invention relates particularly to general formula I or II compounds in which :

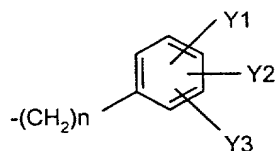
$A_1$  represents an oxygen atom ;

$X_1$  represents a hydrogen and  $X_2$  is a halogen, amino, lower alkyl, hydroxy or  $-NHR_1$  group,

15  $R_1$  being such as previously defined.

$R$  represents :

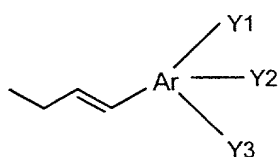
- a lower alkyl, lower alkenyl, aryl alkynyl, 2-, 3- or 4-pyridylalkyl group possibly substituted on the pyridine ring by a lower alkyl, halogen or hydroxy ;



20 in which :

-  $n$  is an integer from 1 to 3,

- Y1, Y2 and Y3 represent each a hydrogen atom or a lower alkoxy group, more particularly methoxy,
- Y1 and Y2 represent each a hydrogen atom and Y3 represents a lower alkoxy group, amino, nitro, hydroxy group,  $-(CH_2)_sCO-Q_1-Q_2-Q_3$  group,  $(CH_2)_s-CN$  group in which,  $Q_1$ ,  $Q_2$ ,  $Q_3$  are such as previously defined, or a lower alkyl possibly substituted by one or several halogen atoms, the particularly preferred of the substituent Y3 being the position 4, or,
- Y1 represents a hydrogen atom and Y2 and Y3, similar or different, represent a hydroxy, halogen or lower alkoxy group, or



in which :

- Ar is such as previously defined ;
- Y1, Y2 and Y3 represent each a hydrogen atom, or
- Y1 and Y2 represent each a hydrogen atom and Y3 is lower alkoxy or halogen ;

$R_4$  and  $R_5$ , represent :

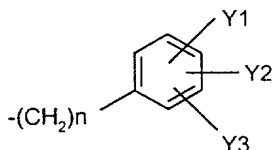
- lower alkyl when  $R_4$  and  $R_5$  are similar, aralkyl, cycloalkyl or cycloalkyl alkyl, when  $R_4$  and  $R_5$  are different,
- lower alkyl,  $R_4$  and  $R_5$  being able to be linked to form a saturated cycle or including one or several double-bonds with one or several heteroatoms chosen among O, S or N and possibly substituted by a lower alkyl, a hydroxy or a lower alkoxy or bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or  $CO-Q_1-Q_2-Q_3$ , two atoms of the cycle then formed may also be part of another cycle chosen among phenyl or heteroaryl comprising from 4 to 8 atoms including 1 to 4 heteroatoms ;

The invention relates more particularly to general formula I compounds in which :

$X_1$  represents a hydrogen atom,

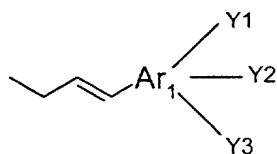
$X_2$  represents a halogen atom, amino, lower alkyl, hydroxy or  $--NHR_1$  ;

5 R represents :



in which :

- n is an integer from 1 to 3,
- Y1, Y2 and Y3 represent each a hydrogen atom or a lower alkoxy group, more particularly methoxy and in particular 3, 4, 5-trimethoxy,
- Y1 and Y2 represent each a hydrogen atom and Y3 represents a lower alkoxy group, amino, nitro, or hydroxy, a lower alkyl group possibly substituted by one or several halogen atoms, a  $-(CH_2)_sCO-Q_1-Q_2-Q_3$  group in which s is 0 or 1,  $Q_1$  is O,  $-NH-$  or a valence bond,  $Q_2$  is  $-(CH_2)_q-$ , q being equal to 0, 1, 2, 3 or 4 and  $Q_3$  is H, OH or  $-NX_3X_4$  in which  $X_3$  and  $X_4$  are such as previously defined, a  $(CH_2)_s-CN$  group in which s is 0 or 1, the position particularly preferred of the substituent Y3 being the position 4, or
- Y1 represents a hydrogen atom and Y2 and Y3, similar or different, represent a hydroxy, halogen or lower alkoxy group; or



in which :

- 
- $Ar_1$  is an aromatic cycle including 6 atoms, one may be a nitrogen atom in position 2, 3 or 4 and preferably in position 3 ;
- Y1, Y2 and Y3 represent each a hydrogen atom, or

- Y1 and Y2 represent each a hydrogen atom and Y3 is a lower alkoxy group or a halogen group when Ar<sub>1</sub> does not include a nitrogen atom; and

R<sub>4</sub> and R<sub>5</sub>, represent :

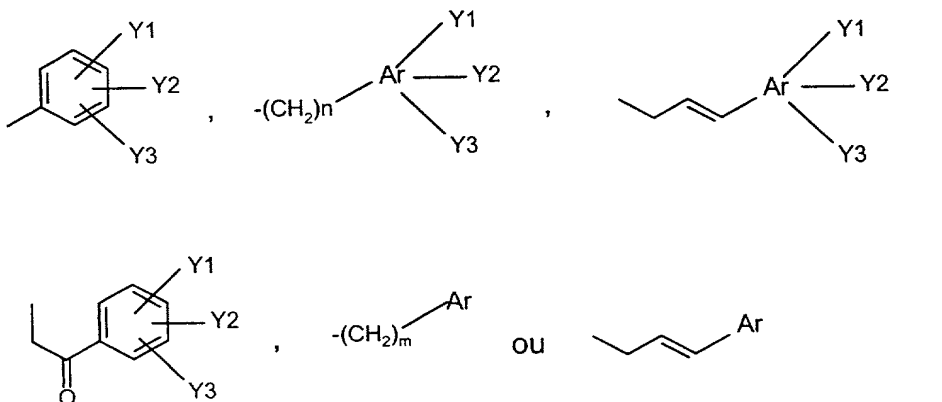
- lower alkyl when R<sub>4</sub> and R<sub>5</sub> are similar, aralkyl, cycloalkyl or cycloalkyl alkyl, when R<sub>4</sub> and R<sub>5</sub> are different,
- lower alkyl, R<sub>4</sub> and R<sub>5</sub> being able to be linked to form a saturated cycle or including one or several double-bonds with one or several heteroatoms chosen among O, S or N and possibly substituted by a lower alkyl, a hydroxy or a lower alkoxy or bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>, two atoms from the cycle then formed may also be part of another cycle chosen among phenyl or heteroaryl comprising from 4 to 8 atoms with 1 to 4 heteroatoms ;

The invention relates also to general formula I or II compounds in which :

X<sub>1</sub>, X<sub>2</sub>, A<sub>1</sub>, R<sub>4</sub> and R<sub>5</sub> are such as previously defined in the summary of the invention ; and

R represents :

- lower alkynyl, aryl alkynyl, 2-, 3- or 4-pyridylalkyl possibly substituted by a lower alkyl, a lower alkoxy, a hydroxy or a halogen group ,



in which :

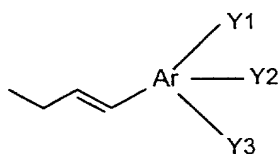
- n is an integer from 1 to 5 and m is an integer from 3 to 5 ;

- Ar is an aromatic cycle including 5 or 6 atoms with 0 to 3 heteroatoms chosen among O, S or N ;
- Y1, Y2 and Y3, similar or different represent :
  - hydroxy, mercapto, amino, nitro, halogen,  $-(CH_2)_sCO-Q_1-Q_2-Q_3$  ,  $(CH_2)_s-CN$ ,  
 in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, possibly substituted by one or several halogen atoms.

In another of its embodiments, the current invention relates to general formula I or II compounds in which :

$X_1$ ,  $X_2$ ,  $R_4$  and  $R_5$  are such as previously defined in the summary of the invention ; and

R represents :



in which :

- Ar is an aromatic cycle including 5 or 6 atoms with 0 to 3 heteroatoms chosen among O, S or N (aromatic cycles including 6 atoms, one atom could be a nitrogen in position 2, 3 or 4, preferably in position 3);
- Y1, Y2 and Y3, similar or different represent :
  - hydrogen, hydroxy, mercapto, amino, nitro, halogen, cyano,  $-(CH_2)_sCO-Q_1-Q_2-Q_3$  in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, possibly substituted by one or several halogen atoms.

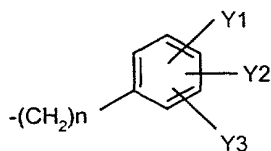
In a preferred manner :

- Y1, Y2 and Y3 represent each a hydrogen atom, or
- Y1 and Y2 represent each a hydrogen atom and Y3 is a lower alkoxy or halogen.

In another of its embodiments, the current invention relates to general formula I or II compounds in which :

$X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are such as previously defined above in the summary of the invention ;  
and

R represents :



in which :

- 10
- $n$  is an integer from 1 to 3 ;
  - $Y_1$ ,  $Y_2$  and  $Y_3$ , similar or different represent :
    - hydroxy, mercapto, amino, nitro, halogen,  $-(CH_2)_sCO-Q_1-Q_2-Q_3$ ,  $(CH_2)_s-CN$   
in which  $s$  is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, possibly substituted by one or several halogen atoms.

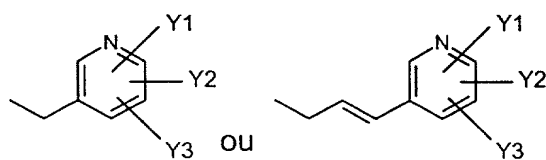
In a preferred manner :

- 15
- $n$  is an integer from 1 to 3,
  - $Y_1$ ,  $Y_2$  and  $Y_3$  represent each a lower alkoxy group, more particularly methoxy and in particular 3, 4, 5-triméthoxy,
  - $Y_1$  and  $Y_2$  represent each a hydrogen atom and  $Y_3$  represents a lower alkoxy group, cyano, amino, nitro or hydroxy, a lower alkyl group possibly substituted  
20 by one or several halogen atoms or a  $-(CH_2)_sCO-Q_1-Q_2-Q_3$  group in which  $s$  is 0 or 1,  $Q_1$  is O,  $-NH-$  or a valence bond,  $Q_2$  is  $-(CH_2)_q-$ ,  $q$  being equal to 0, 1, 2, 3 or 4 and  $Q_3$  is H, OH or  $-NX_3X_4$  in which  $X_3$  and  $X_4$  are such as previously defined, the position particularly preferred of substituent  $Y_3$  being position 4, or  
25  $Y_1$  represents a hydrogen atom and  $Y_2$  and  $Y_3$ , similar or different, represent a hydroxy, halogen or lower alkoxy group.

In another of its embodiments, the current invention relates to general formula I or II compounds in which

30  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are such as previously defined in the summary of the invention; and

R represents :



in which :

- 5
- Y1, Y2 and Y3, similar or different represent :
    - hydrogen, hydroxy, mercapto, amino, nitro, halogen,  $-(CH_2)_sCO-Q_1-Q_2-Q_3$ ,  $(CH_2)_s-CN$ , in which s is an integer from 0 to 6, lower alkyl, lower alkoxy or lower thioalkyl, possibly substituted by one or several halogen atoms.

10 In a preferred manner :

- Y1, Y2 and Y3 represent each a hydrogen atom, or
- Y1 and Y2 represent each a hydrogen atom and Y3 is lower alkoxy or halogen.

15 In another of its embodiments, the current invention relates to general formula I or II compounds in which

$X_1$ ,  $X_2$ ,  $A_1$ , R,  $R_4$  and  $R_5$  are such as previously defined in the summary of the invention; and

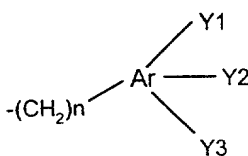
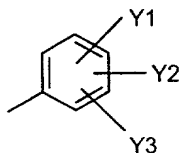
- 20
- when  $X_1$  and  $X_2$  represent hydrogen, R is not alkyl, phenyl, benzyl or allyl ,
  - when  $X_1$  represents hydrogen and  $X_2$  represents 7-Cl or  $CH_3$ , R is not alkyl ; and
  - when  $X_1$  represents hydrogen,  $X_2$  is not 8-Cl.

The invention relates also to a group of a formula I or II compounds particularly active as  $TNF\alpha$  inhibitors and in which :

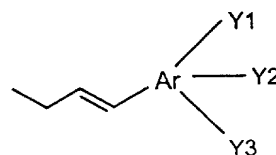
- 25
- $A_1$  is O or S ;
  - $X_1$  and  $X_2$ , similar or different, represent :
    - hydrogen, hydroxy, halogen, amino, nitro, mercapto, cyano, carboxy,
    - lower alkyl, lower alkoxy or  $-S(O)_mR_8$  in which m is 0, 1 or 2 and  $R_8$  is lower alkyl, possibly substituted by one or several halogen atoms.
- 30
- In a preferred manner,  $X_1$  is H and  $X_2$  is halogen, notably 7-Br, or lower alkyl, notably 7- $CH_3$ .



- R represents:



ou



in which :

- n is an integer from 1 to 5,
- Ar is an aromatic cycle including 5 or 6 atoms with 0 to 3 heteroatoms chosen among O, S or N,
- Y1, Y2 and Y3, similar or different represent :
  - hydrogen, hydroxy, mercapto, amino, nitro, halogen,  $-(CH_2)_sCO-Q_1-Q_2-Q_3$ ,  $(CH_2)_s-CN$  in which s is an integer from 0 to 6 ;
  - lower alkyl, lower alkoxy or  $-S(O)_mR_8$  in which m is 0, 1 or 2 and  $R_8$  is a lower alkyl, possibly substituted by one or several halogen atoms.

The substituents particularly preferred forming the group R include cinnamyl, 3-pyridyl allyl, paracyano benzyl, dimethoxy benzyl and 3-pyridyl méthyl.

- $R_4$  and  $R_5$ , similar or different, represent :
 

lower alkyl,  $R_4$  and  $R_5$  being able to be linked to form a saturated cycle or including one or several double-bonds with one or several heteroatoms chosen among O, S or N and possibly bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or  $CO-Q_1-Q_2-Q_3$ . substituents particularly preferred forming the group  $NR_4R_5$  include dimethylamino, pyrrolidine and azepanyl.

Compounds particularly preferred as  $TNF\alpha$  inhibitors include the following molecules :

- 3 7-Bromo-1-dimethylamino-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 104 1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 94 4-(3,4-Dimethoxy-benzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 101 4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 85 7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 98 7-Methyl-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 91 1-Azepan-1-yl-7-methyl-4-pyridin-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 93 4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 103 1-Dimethylamino-7-methyl-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 46 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 35 1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Among the groups defined above, the following substituents are particularly preferred :

- In a general manner for groups X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> :

- halogen : F, Cl, Br, I, preferably Br and Cl,
- lower alkyl : linear or branched including 1 to 6, preferably 1 to 3 carbon atoms,
- lower alkoxy : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms,
- lower alkylthio : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms,

- lower alkenyl : comprising from 3 to 6, preferably 3 to 4 carbon atoms, more particularly allyl ,
- lower alkynyl : comprising from 3 to 9 carbon atoms, more particularly propargyl and phenyl-propargyl ,
- 2-, 3- or 4-pyridylalkyl in which alkyl includes from 1 to 5, preferably 1 to 3 carbon atoms,
- aryl : comprising from 5 to 8, preferably 5 or 6 atoms,
- aralkyl in which alkyl includes from 1 to 6, preferably 1 to 4 carbon atoms,
- cycloalkyl : including 3 to 8, preferably 3 to 6 carbon atoms,
- cycloalkyl alkyl in which alkyl includes from 1 to 6, preferably 1 to 3 atoms de carbone and cycloalkyl include from 3 to 8, de preferably 3 to 6 carbon atoms ,
- lower alkyl, lower alkoxy or lower alkylthio possibly substituted by one or several halogen atoms : we will prefer trisubstituted groups of type  $-(CH_2)_p-CF_3$ ,  $-O-(CH_2)_p-CF_3$  or  $-S-(CH_2)_p-CF_3$ , in which p is an integer from 0 to 3.
- In particular manner for the groups  $X_1$  and  $X_2$  :
  - $-NH-R_1$ , or  $-NR_2R_3$  : when lower alkyl is substituted by one or several groups chosen among halogen, hydroxy, cyano, lower alkoxy or  $CO-Q_1-Q_2-Q_3$ , the substituents number varies between 1 and 4, preferably between 1 and 2,
  - $-NR_2R_3$  : when  $R_2$  and  $R_3$  are bound to form a cycle, this cycle is characterized as including preferably :
    - between 1 and 4, more particularly between 1 and 2 heteroatoms chosen among O, S or N, the cyclic substituents of this type being, in a preferred manner, saturated cycles of type  $C_mN$  in which m is an integer from 2 to 7, preferably 4 to 6, particularly preferred cycles being chosen among group including pyrrolidine, piperidine, homopiperidine or cyclooctylamine and
    - between 0 and 4, in a preferred manner between 0 and 2, more particularly between 1 and 2 substituents chosen among hydroxy, keto, lower alkyl, lower alkoxy or  $-CO-Q_1-Q_2-Q_3$ ,
  - groups  $X_1$  and  $X_2$  are particularly localized in position 7 and 8 of aromatic cycle for formula I and II compounds to which they are bound.
- In particular manner for the group R :

- the substituents Y1, Y2 and Y3 are particularly localized in position 3 and/or 4 of the aromatic cycle to which they are bound.

- In particular manner for the groups R<sub>4</sub> and R<sub>5</sub> :

- 5 - when R<sub>4</sub> and R<sub>5</sub> are bound to form a cycle, this cycle is characterized as preferably including :
  - between 1 and 4 heteroatoms chosen among O, S or N, cyclic substituents of this type being, in a preferred manner, saturated cycles of type C<sub>m</sub>N, m being an integer between 2 and 7, cycles particularly preferred being chosen among group  
10 including pyrrolidine, piperidine, homopiperidine or cyclooctylamine, and
  - between 0 and 4, in a preferred manner between 0 and 2 substituents chosen among hydroxy, keto, lower alkyl, lower alkoxy or -CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>.

Among the preferred compounds of the current invention, we find the following  
15 compounds :

- 1     1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 2     1-(azepan-1-yl)-7-chloro-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 3     7-Bromo-1-dimethylamino-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 4     7-Bromo-4-pyridin-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 5     7-Bromo-3-pyridin-3-ylmethyl-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 6     1-Azepan-1-yl-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 7     1-(azepan-1-yl)-7-chloro-4-allyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 8     1-(azepan-1-yl)-7-chloro-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 9     1-(azepan-1-yl)-7-chloro-4-(2-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 10    1-(azepan-1-yl)-7-chloro-4-(3-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 11    1-(azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 12    1-(azepan-1-yl)-7-chloro-4-(4-bromobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 13    1-(azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 14    1-(azepan-1-yl)-7-chloro-4-(4-(trifluoromethyl)benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 15    1-(azepan-1-yl)-7-chloro-4-(4-cyanobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 16    1-(azepan-1-yl)-7-chloro-4-(2-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 17    1-(azepan-1-yl)-7-chloro-4-(3-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

- 18 1-(azepan-1-yl)-7-chloro-4-(4-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 19 1-(azepan-1-yl)-7-chloro-4-(3,4-dichlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 20 1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 21 1-(azepan-1-yl)-7-chloro-4-(2-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 22 1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 23 1-(azepan-1-yl)-7-chloro-4-(4-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 24 1-(azepan-1-yl)-7-chloro-4-(2-phenylthyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 25 1-(azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)ethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 26 1-(azepan-1-yl)-7-chloro-4-(3-phenylpropyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 27 1-Azepan-1-yl-7-chloro-4-(2-oxo-2-phenyl-ethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 28 1-(azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 29 1-(azepan-1-yl)-7-chloro-4-[2-(4-chlorophenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 30 5-[(1-(azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)acetyl]-2-methoxybenzoic acid methyl ester
- 31 7-Chloro-4-pyridin-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 32 1-(azepan-1-yl)-7-bromo-4-(4-chloro-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 33 1-Azepan-1-yl-7-bromo-4-(4-fluoro-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 34 4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

- 35 1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 36 1-(azepan-1-yl)-7-bromo-4-(3-pyridinylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 37 1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 38 1-Azepan-1-yl-7-bromo-4-[3-(4-chloro-phenyl)-allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 39 1-Azepan-1-yl-7-bromo-4-[3-(4-methoxy-phenyl)-allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 40 1-Azepan-1-yl-7-bromo-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 41 1-Azepan-1-yl-7-bromo-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 42 7-Bromo-4-(4-methyl-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 43 7-Bromo-4-(4-chloro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 44 7-Bromo-4-(4-fluoro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 45 3-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 46 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 47 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester
- 48 7-Bromo-4-(4-nitro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 49 7-Bromo-4-(4-methoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 50 Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl ester
- 51 7-Bromo-4-(4-hydroxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

- 52 7-Bromo-4-(3,4-dimethoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 53 4-Benzo[1,3]dioxol-5-ylmethyl-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 54 7-Bromo-4-(3,5-dimethoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 55 7-Bromo-1-pyrrolidin-1-yl-4-(3,4,5-trimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 56 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid
- 57 1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 58 7-Bromo-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 59 7-Bromo-4-[(E)-3-(4-chloro-phenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 60 7-Bromo-4-[3-(4-methoxy-phenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 61 7-Bromo-4-(3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 62 7-Bromo-4-((E)-3-pyridin-4-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 63 7-Bromo-4-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 64 7-Bromo-4-(3,5-dimethyl-isoxazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 65 7-Bromo-4-cyclopentylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 66 7-Bromo-4-butyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 67 7-Bromo-1-pyrrolidin-1-yl-4-(2,2,2-trifluoro-ethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 68 7-Bromo-4-(2-hydroxy-ethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one



- 69 7-Bromo-4-(2-diethylamino-ethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 70 7-Bromo-4-prop-2-ynyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 71 7-Bromo-4-(2-phenoxy-ethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 72 7-Bromo-4-(2-phenylsulfényl-ethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 73 (7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)-phenyl-acetic acid methyl ester
- 74 4-(7-Bromo-5-oxo-1-piperidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 75 7-Bromo-4-(3,4-dimethoxy-benzyl)-1-piperidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 76 1-(piperidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 77 7-Bromo-4-(3-pyridin-3-yl-allyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 78 Bromo-dimethylamino-(4-methyl-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 80 7-Bromo-1-dimethylamino-4-(4-hydroxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 81 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester
- 82 [4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid
- 83 [4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetonitrile
- 84 7-Bromo-1-dimethylamino-4-pyridin-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 85 7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

- 86 7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 87 7-Bromo-1-dimethylamino-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 88 7-Bromo-1-dimethylamino-4-prop-2-ynyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 89 7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 90 (7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)-phenyl-acetic acid methyl ester
- 91 1-Azepan-1-yl-7-methyl-4-pyridin-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 92 1-Azepan-1-yl-7-methyl-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 93 4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 94 4-(3,4-Dimethoxy-benzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 95 4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester
- 96 [4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid
- 97 7-Methyl-4-pyridin-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 98 7-Methyl-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 99 [4-(7-Methyl-5-oxo-1-thiomorpholin-4-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid
- 100 7-Methyl-4-(3-pyridin-3-yl-allyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 101 4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 102 [4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

- 103 1-Dimethylamino-7-methyl-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 104 1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 105 1-Dimethylamino-7-methyl-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 106 1-(azepan-1-yl)-8-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 107 4-(4-Cyano-benzyl)-1-dimethylamino-5-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-carbonitrile
- 108 7-Hydroxy-4-((E)-3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 109 1-(azepan-1-yl)-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 110 3-Allyl-1-azepan-1-yl-7-chloro-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 111 1-(azepan-1-yl)-7-chloro-3-benzyl-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 112 1-Azepan-1-yl-7-chloro-3-(4-methyl-benzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 113 1-(azepan-1-yl)-7-chloro-3-(2-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 114 1-(azepan-1-yl)-7-chloro-3-(3-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 115 1-(azepan-1-yl)-7-chloro-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 116 1-(azepan-1-yl)-7-chloro-3-(4-bromobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 117 1-(azepan-1-yl)-7-chloro-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 118 1-(azepan-1-yl)-7-chloro-3-(4-(trifluoromethyl)benzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 119 1-(azepan-1-yl)-7-chloro-3-(4-cyanobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

- 120 1-(azepan-1-yl)-7-chloro-3-(2-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 121 1-(azepan-1-yl)-7-chloro-3-(3-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 122 1-(azepan-1-yl)-7-chloro-3-(4-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 123 1-(azepan-1-yl)-7-chloro-3-(3,4-dichlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 124 1-(azepan-1-yl)-7-chloro-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 125 1-(azepan-1-yl)-7-chloro-3-(2-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 126 1-(azepan-1-yl)-7-chloro-3-(3-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 127 1-(azepan-1-yl)-7-chloro-3-(2-phenylthyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 128 1-(azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)ethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 129 1-(azepan-1-yl)-7-chloro-3-(3-phenylpropyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 130 1-Azepan-1-yl-7-chloro-3-(2-oxo-2-phenyl-ethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 131 1-(azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 132 1-(azepan-1-yl)-7-chloro-3-[2-(4-chlorophenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 133 5-[(1-(azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]-quinazolin-3-yl)acetyl]-2-methoxybenzoic acid methyl ester
- 134 1-(azepan-1-yl)-7-bromo-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 135 1-(azepan-1-yl)-7-bromo-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 136 4-(1-(azepan-1-yl)-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]-quinazolin-3-ylmethyl)- benzonitrile

- 137 1-(azepan-1-yl)-7-bromo-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 138 [4-(7-Bromo-5-oxo-1-perhydro-azepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-phenyl]-acetic acid
- 139 1-(azepan-1-yl)-7-bromo-3-(pyridin-3-ylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 140 1-Azepan-1-yl-7-bromo-3-((E)-3-phenyl-allyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 141 7-Bromo-3-((E)-3-phenyl-allyl)-1-piperidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 142 7-bromo-3-(4-chlorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 143 7-bromo-3-(4-fluorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 144 4-(7-bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]-quinazolin-3-ylmethyl)- benzonitrile
- 145 4-(7-bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]-quinazolin-3-ylmethyl)benzoic acid methyl ester
- 146 7-Bromo-3-(4-methoxy-benzyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 147 Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-phenyl ester
- 148 7-Bromo-1-dimethylamino-3-(4-hydroxy-benzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 149 3-(benzo[1,3]dioxol-5-ylmethyl)-7-bromo-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 150 7-bromo-3-(3,5-dimethoxy-benzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo- [4,3-a]quinazolin-5-one
- 151 7-bromo-1-(pyrrolidin-1-yl)-3-(3,4,5-trimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 152 7-Bromo-3-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 153 7-bromo-3-(n-butyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

- 154 (7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)-phenyl-acetic acid methyl ester
- 155 7-Bromo-1-dimethylamino-3-(3-phenyl-allyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 156 (7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)-phenyl-acetic acid methyl ester
- 157 1-(azepan-1-yl)-7-methyl-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 158 7-methyl-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 159 1-(azepan-1-yl)-3,8-dimethyl-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 160 1-Azepan-1-yl-8-methyl-3-((E)-3-phenyl-allyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 161 7-hydroxy-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 162 1,8-bis(azepan-1-yl)-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 163 1-(azepan-1-yl)-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 164 4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 165 4-Benzyl-7-bromo-1-(butyl-methyl-amino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 166 4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 167 7-chloro-1-dibutylamino-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 168 7-chloro-4-methyl-1-(piperidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 169 7-Chloro-4-methyl-1-(4-methyl-piperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 170 7-Chloro-4-methyl-1-(1,8,8-trimethyl-3-aza-bicyclo[3.2.1]oct-3-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

- 171 1-(azepan-1-yl)-7-chloro-4-phenyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 172 1-(azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 173 4-benzyl-7-chloro-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 174 4-benzyl-7-chloro-1-(piperidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 175 1-(azepan-1-yl)-8-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 176 1-(azepan-1-yl)-4-benzyl-8-chloro-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 177 1-(azepan-1-yl)-7-bromo-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 178 4-benzyl-7-bromo-1-(piperidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 179 4-Benzyl-7-bromo-1-dimethylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 180 4-Benzyl-7-bromo-1-morpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 181 4-Benzyl-7-bromo-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 182 4-Benzyl-7-bromo-1-(4-methyl-piperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 183 4-Benzyl-7-bromo-1-(4-phenyl-piperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 184 4-Benzyl-1-(4-benzyl-piperazin-1-yl)-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 185 4-Benzyl-7-bromo-1-(3,6-dihydro-2H-pyridin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 186 4-Benzyl-7-bromo-1-(2,5-dihydro-pyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 187 4-Benzyl-7-bromo-1-(3-hydroxy-pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

- 188 4-Benzyl-7-bromo-1-methylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 189 4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 190 1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 191 4-Benzyl-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 192 4-Benzyl-1-dimethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 193 4-Benzyl-7-methyl-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 194 1-Azepan-1-yl-4-benzyl-8-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 195 1-Azepan-1-yl-4-benzyl-7-methoxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 196 4-Benzyl-7-methoxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 197 4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile
- 198 1-Azepan-1-yl-4-benzyl-7-nitro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 199 1-(azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 200 1-(azepan-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 201 1-(azepan-1-yl)-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 202 1-(azepan-1-yl)-6-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 203 1-(azepan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 204 1-(azepan-1-yl)-7-chloro-4-ethyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one



- 205 7-chloro-4-methyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 206 7-chloro-4-methyl-1-(morpholin-4-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 207 1-(azocan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 208 7-chloro-1-(3,4-dihydro-2H-quinolin-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 209 7-chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 210 1-(4-benzylpiperidin-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 211 7-chloro-4-methyl-1-(1,3,3-trimethyl-6-azabicyclo[3,2,1]oct-6-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 212 1-(azepan-1-yl)-7-fluoro-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 213 1-(azepan-1-yl)-7-iodo-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 214 1-(azepan-1-yl)-7-methoxy-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one
- 215 4-Benzyl-7-bromo-1-(ethyl-methyl-amino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 216 4-Benzyl-1-diethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 217 4-Benzyl-7-bromo-1-pyrrol-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 218 4-(4-Amino-benzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 219 4-Benzyl-7-hydroxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 220 4-(7-Hydroxy-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 221 N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl)-acetamide

- 222 N-[5-Oxo-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl]-acetamide
- 223 7-Amino-4-((E)-3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 224 7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 225 7-Amino-4-benzyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 226 4-(7-Amino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 227 7-Amino-4-((E)-3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 228 4-(7-Amino-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 229 7-Amino-1-dimethylamino-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 230 4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 231 4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 232 4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 233 4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 234 4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 235 N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl)-methanesulfonamide
- 236 4-Benzyl-7-dimethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 237 4-Benzyl-1-dimethylamino-5-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile
- 238 4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carboxylic acid

- 239 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid methyl ester
- 240 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methyl-acetamide
- 241 2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetamide
- 242 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethyl-acetamide
- 243 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-hydroxy-acetamide
- 244 4-(1-Dimethylamino-7-methyl-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 245 4-(7-Bromo-1-dimethylamino-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 246 1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione
- 247 4-benzyl-7-(N,N-dimethylsulfonylamino)-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo [4,3-a] quinazolin-5-one

Among the compounds mentioned above, the following compounds are preferred :

- 1 1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 3 7-Bromo-1-dimethylamino-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 11 1-(azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 13 1-(azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 20 1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 22 1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 32 1-(azepan-1-yl)-7-bromo-4-(4-chlorophenylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 34 4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 35 1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 37 1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 40 1-Azepan-1-yl-7-bromo-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 41 1-Azepan-1-yl-7-bromo-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 42 7-Bromo-4-(4-methyl-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 43 7-Bromo-4-(4-chloro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 44 7-Bromo-4-(4-fluoro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 46 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 47 4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester

- 48 7-Bromo-4-(4-nitro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 49 7-Bromo-4-(4-methoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 50 Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl ester
- 51 7-Bromo-4-(4-hydroxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 52 7-Bromo-4-(3,4-dimethoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 57 1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 59 7-Bromo-4-[(E)-3-(4-chloro-phenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 60 7-Bromo-4-[3-(4-methoxy-phenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 61 7-Bromo-4-(3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 62 7-Bromo-4-((E)-3-pyridin-4-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 75 7-Bromo-4-(3,4-dimethoxy-benzyl)-1-piperidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 76 1-(piperidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 78 7-Bromo-1-dimethylamino-4-(4-methyl-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 80 7-Bromo-1-dimethylamino-4-(4-hydroxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 81 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester
- 83 [4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetonitrile

- 85 7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 89 7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 92 1-Azepan-1-yl-7-methyl-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 94 4-(3,4-Dimethoxy-benzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 96 [4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid
- 98 7-Methyl-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 102 [4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid
- 103 1-Dimethylamino-7-methyl-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 104 1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 138 [4-(7-Bromo-5-oxo-1-perhydro-azepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-phenyl]-acetic acid
- 164 4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 186 4-Benzyl-7-bromo-1-(2,5-dihydro-pyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 189 4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 190 1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 218 4-(4-Amino-benzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 223 7-Amino-4-((E)-3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 224 7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

- 227 7-Amino-4-((E)-3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 229 7-Amino-1-dimethylamino-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 230 4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 231 4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 232 4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 233 4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 234 4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 239 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid methyl ester
- 240 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methyl-acetamide
- 241 2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetamide
- 242 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethyl-acetamide
- 243 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-hydroxy-acetamide
- 246 1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

Among the compounds mentioned above, the following compounds are preferred :

- 3 7-Bromo-1-dimethylamino-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 20 1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 22 1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 34 4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 35 1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 37 1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 40 1-Azepan-1-yl-7-bromo-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 41 1-Azepan-1-yl-7-bromo-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 42 7-Bromo-4-(4-methyl-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 43 7-Bromo-4-(4-chloro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 52 7-Bromo-4-(3,4-dimethoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 57 1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 61 7-Bromo-4-(3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 76 1-(piperidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 79 4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 81 4-(Bromo-dimethylamino-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester
- 85 7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one



- 89 7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 92 1-Azepan-1-yl-7-methyl-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 94 4-(3,4-Dimethoxy-benzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 98 7-Methyl-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 223 7-Amino-4-((E)-3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 227 7-Amino-4-((E)-3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 230 4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one
- 231 4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile
- 239 [4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid methyl ester
- 240 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methyl-acetamide
- 242 2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethyl-acetamide
- 246 1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

The invention relates also to salts acceptable in pharmacy of a formula I or II compounds. We will find a review of pharmacologically acceptable salts in J. Pharm. Sci., 1977, 66, 1-19.

- 5 However, by a pharmacologically acceptable salt of a formula I or II compound presenting a basic function, we mean the addition salt of a formula I or II compounds from non toxic inorganic or organic acids as for example salts of hydrobromic, hydrochloric, sulfuric, phosphoric, nitric, acetic, succinic, tartaric, citric, maleic, hydroxymaleic, benzoic, fumaric, toluene-sulfonic, isethionic acids and others. Various salts of quaternary ammonium of I or II
- 10 formula are also included in category compounds of this invention. And by pharmacologically

acceptable salts of a formula I or II compound presenting an acid function, we mean usual salts of a formula I or II compounds made from non-toxic mineral or organic bases as for example hydroxides of alkaline and alkaline earth metals (sodium, potassium, magnesium and calcium), amines (dibenzylethylmethanamine, trimethylamine, piperidine, pyrrolidine, benzylamine and others) or also quaternary ammonium hydroxides like tetramethylammonium hydroxide.

As previously mentioned, formula I and II compounds of the current invention are inhibitors of phosphodiesterase enzyme and particularly of phosphodiesterase 4 (PDE4) enzyme.

Consequently, their use is recommended for treatment of diseases or affections relying on therapy by PDE4 inhibition. As an example, compounds of the current invention can be recommended for treatment of septicemia, polyvisceral deficiency, asthma, chronic bronchitis, emphysema, chronic obstructive pneumopathy (or COPD), allergic rhinitis, atopic dermatitis, pulmonary high blood pressure, cardiac or pulmonary insufficiency, congestive cardiac insufficiency, psoriasis, inflammatory diseases of the digestive system such as hemorrhagic rectocolitis and Crohn's disease, diseases linked to elevated TNF- $\alpha$  levels such as acute respiratory distress syndrome in the adult and acute pancreatitis, rheumatoid arthritis, osteoporosis, multiple sclerosis and depression.

PDE4 inhibitors of the current invention may also be used for treatment of acute pulmonary attack, neuronal attack caused by ischemia (ischemia-induced neuronal damage), diabetes, chronic lymphoid leukemia, and to attenuate development of tolerance or dependence phenomena to morphine. Compounds of the invention may also contribute to decreasing memory loss of behavior (behavioral memory) such as observed for example in patients suffering from Alzheimer's disease.

We may also consider use of the compounds of the current invention in the fields of urology, more particularly in treatment of prostate disease such as benign hypertrophy of the prostate or for prevention of premature child birth, for example by inhibition of contraction triggering before term, preferably by PDE4 inhibitor action on myometrium.

### Structure-activity analysis of formula I and II compounds

The inventors, wishing not to be bound in a formal manner to a definitive theory, agree that structural parameters mentioned below may be considered in order to guide the person skilled in the art in the choice of substituents combination which, beyond preferred compounds disclosed in the current application, may allow not only an optimization of the PDE4 inhibitor

activity, but also a better optimization of important additional parameters such as solubility, biodegradability and toxicity of considered compounds.

First, the inventors consider that the catalytic site of the enzyme PDE4 is of a sufficiently large size to globally accommodate a fairly wide range of structural changes in substituents of the compounds of the invention which can bind to this site. In this respect, the inventors consider that compounds of the current invention have probably the capacity to interact at least on three distinct points of the catalytic site of the isoenzyme PDE4. One first interaction point may be localized on the aromatic ring including the substituents  $X_1$  and  $X_2$ . A second interaction point is probably localized on substituent R while a third interaction point is probably localized on group  $NR_4R_5$ . Potential functionality of each binding point is suggested below.

However, it is important to precise here that interaction points mentioned above are not necessarily classified by increasing or decreasing importance order relating to their incidence on inhibitory activity of invention compounds. In fact, it seems possible that each interaction point participates in a different manner in global pharmacological properties of these compounds.

The first interaction point mentioned previously may be localized then on the aromatic ring including substituents  $X_1$  and  $X_2$ . This aromatic ring may participate to the invention compound binding to enzyme PDE4 catalytic site, it seems possible to modulate this binding by substituents  $X_1$  and  $X_2$  choice.

Experiments performed up-to-date by the inventors tend to demonstrate that substituents  $X_1$  and  $X_2$  currently preferred are those for which  $X_1$  is hydrogen and  $X_2$  is chosen among halogen, more particularly Br and Cl, methyl, hydroxy, amino and alkylamino. We establish then that among preferred substituents  $X_2$ , we simultaneously find some donors (e.g. methyl) and some attractors (e.g. Br, Cl) of electrons. It seems then unlikely that  $X_2$  could be chosen solely according to electronic properties of the recommended substituent. The inventors agree that important selection criteria are placed initially on substituent position in the aromatic ring and therefore on the level of some parameters such as substituent steric congestion or presence of donor atom or proton acceptor.

However, it seems established that substituents  $X_1$  and  $X_2$  position on the aromatic ring could have an influence on final activity of invention compounds. As an example, compounds including a substituent other than hydrogen in position 7 are generally more active than the same compounds including this substituent in position 8. Thus it seems probable that choice and position of substituents  $X_1$  and  $X_2$  allow to move the aromatic ring inside the cavity of the PDE4 catalytic site and consequently to modulate inhibitory activity of invention compounds. Moreover, it seems that compounds including a substituent in position 7 are more selective of sub-type PDE4 compared to the other isoenzymes PDE5, PDE3 and PDE1 than compounds including a substituent in position 8. These latter have a PDE4 inhibitory activity (although less) but they seem less selective compared to the other isoenzymes. However, it seems clearly also that although  $X_1$  and  $X_2$  could be chosen among an outstanding number of substituents, we will obtain a better tolerance for this choice if substituent R is well targeted.

The second interaction point of compounds of the current invention with the enzyme PDE4 will be localized on the substituent R. The inventors reckon that it concerns presumably of the most important anchorage point of the molecule to the enzyme. It seems indeed probable that this second interaction is localized in a large cavity inside the PDE4 catalytic site. It is then essential that the substituent R can be anchored to the catalytic site. However, the choice of groups included in the definition of R given above, seems to demonstrate some flexibility on R anchorage to this second binding site. Therefore, it could be possible to obtain a PDE4 inhibitory activity with compounds having rather different substituents R from a structural point of view. As an example, we will prefer the use of a substituent including an aromatic ring, preferably substituted itself, and separated from the principal heterocycle by a chain including between 1 and 4 atoms, particularly some carbon atoms, the said substituent presenting a relatively variable spatial orientation. This observation seems to open the way to the possibility to modulate in a more subtle manner the global properties of invention compounds.

The inventors agree indeed that although substituent R remains most probably a determinant element on PDE4 inhibitory activity of invention compounds, it is probably possible to make it vary and then act on the important extra pharmacological parameters without altering this inhibitory activity in a substantial manner. As an example, some compounds including in substituent R a group  $-\text{CH}_2\text{CH}=\text{CH}-\text{C}_6\text{H}_5$  or a substituted benzyl group, preferably in

position 4 (other substituents being identical for the two compounds), have PDE4 inhibitory activity of same magnitude order.

The third interaction site of the compounds of the invention on PDE4 is localized presumably on group  $-NR_4R_5$ . The inventors agree that it concerns probably a binding site much more specific than the two sites disclosed above although substituent R moving in the enzymatic cavity may however influence on specificity of this third site. Compounds of the invention having the best inhibitory activities are those for which  $R_4$  and  $R_5$ , which represent each a lower alkyl, are bound to form a cycle, preferably including between 5 and 8 carbon atoms, more particularly a cycle with 5 or 7 carbon atoms. The skilled person's scope for manoeuvre on this group's variation seems then more limited.

In summary, experimentation performed by the inventors with compounds of the current invention seem to demonstrate that the size of PDE4 catalytic site is large enough to accommodate several structural changes on the three binding sites disclosed previously. However, the most important handling margin seems anyway to be localized on the substituent R variation.

#### **Galenic formulation of the invention compounds**

The compounds of the invention are administrated as an appropriate composition accordingly to the nature and the scale of the disease to treat. The daily posology in humans is usually between 2 mg and 1 g of product that can be absorbed in one or several intakes. The compositions are prepared by usual methods for the skilled man and contain in a general manner 0.5 to 60 % by weight of active principle (formula I compounds) and 40 to 99.5 % by weight of appropriate pharmaceutical carrier.

The compositions of the current invention are then prepared under forms compatible with the desired administering route. As an example, the following pharmaceutical forms may be considered, although the listing provided below is not limiting:

Forms for administering by oral route :

Drinkable solutions, suspensions, powder sachets for drinkable solution, capsules, gastro-resistant capsules, prolonged-release forms, emulsions, HPMR capsules, lyophilisates to melt beneath the tongue.

5

1) Forms for administering by parenteral route :

Intravenous route :

Aqueous solutions, solutions water / co-solvent, solutions using one or several solubilizing agents, colloidal suspensions, emulsions, nano-particle suspensions usable for injection of long-lasting release forms, diffuse forms and liposomes.

10

Subcutaneous / intra-muscular route :

In addition, forms usable as intravenous route which are also usable for subcutaneous and intra-muscular routes, other form types such as suspensions, diffused forms, long-lasting release colloids as well as long-lasting release implants can also be used.

15

2) Forms for administering by topic route :

Among the most used topic forms, we distinguish creams, colloids (aqueous phases jellified by polymers), patches, which are dressings to stick directly on skin and which can be used to treat dermatitis without percutaneous penetration of the active substance, sprays, emulsions and solutions.

20

3) Forms for administering by pulmonary route :

In this category we distinguish forms of solutions for aerosols, powders for inhaling apparatus, and other appropriate forms.

25

4) Forms for administering by nasal route :

It concerns mainly here solutions for drops.

5) Forms for administering by rectal route :

We will note amongst others suppositories and colloids.

30

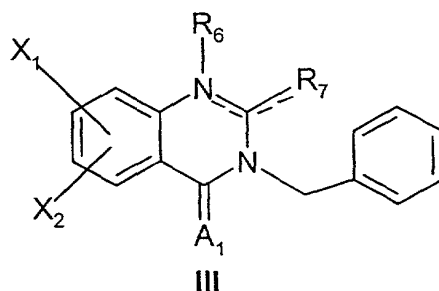
We can also consider the use of forms allowing ophthalmic solution administering or allowing administering of active principle by vaginal route.

Another important category of pharmaceutical form, which can be used in the context of the current invention, relates to forms allowing improvement in solubility of the active principle. As an example, we can consider the use of aqueous solutions of cyclodextrin, and more particularly forms including hydroxypropyl beta cyclodextrin. A detailed review of this type of pharmaceutical form is presented in an article issued in the *Journal of Pharmaceutical Sciences*, 1142-1169, 85 (11), 1996, and incorporated herein by.

Different pharmaceutical forms recommended above are disclosed in a detailed manner in the book « Pharmacie galénique » by A. LEHIR (ed. Masson, 1992 (6<sup>th</sup> edition) incorporated reference.

### Intermediaries compounds

The current invention relates also to general formula III intermediaries compounds :



in which X<sub>1</sub>, X<sub>2</sub>, A<sub>1</sub>, R<sub>6</sub> and R<sub>7</sub> are such as previously defined.

The invention relates particularly to general formula III intermediaries compounds in which :

X<sub>1</sub> and X<sub>2</sub> are such as previously defined, and

R<sub>7</sub> is bound to nitrogen in R<sub>6</sub> to form a triazol, substituted in position 1 by a Br, Cl, mercapto or lower thioalkyl group preferably CH<sub>3</sub>-S-.

Among the groups defined above the following substituents are particularly preferred :

- In a general manner for the groups X<sub>1</sub>, X<sub>2</sub>, R<sub>6</sub> and R<sub>7</sub> :
- halogen : F, Cl, Br, I, preferably Br and Cl,

- lower alkyl : linear or branched comprising from 1 to 6, preferably from 1 to 3 carbon atoms ,

- lower alkoxy : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms ,

5 - lower thioalkyl : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms .

- In particular manner for the groups  $X_1$  and  $X_2$  :

$X_1$  and  $X_2$  are particularly localized in position 6 and 7 of the main quinazolinone cycle.

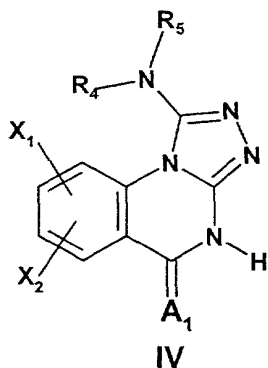
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- In particular manner for the groups  $R_6$  and  $R_7$  :

when  $R_7$  is bound to the nitrogen in  $R_6$  to form a cycle, the formed cycle is preferably a triazole, substituted in position 1 by a group Br, Cl, mercapto or lower thioalkyl, preferably  $CH_3-S-$ .

15

A second series of intermediaries includes the following general formula IV compounds:



in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are such as previously defined.

20 For the groups as above, the following substituents are particularly preferred :

- In a general manner for the groups  $X_1$ ,  $X_2$ ,  $R_4$  and  $R_5$  :

- halogen : F, Cl, Br, I, preferably Br and Cl,

- lower alkyl : linear or branched comprising from 1 to 6, preferably 1 to 3 carbon atoms ,

25 - lower alkyl : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms ,



- lower alkyl,  $R_4$  and  $R_5$  being able to be linked to form a saturated cycle or including one or several double-bonds including one or several heteroatoms chosen among O, S or N and possibly bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or  $CO-Q_1-Q_2-Q_3$ , two atoms of the cycle then formed could also be part of another cycle chosen among phenyl or heteroaryl comprising from 4 to 8 atoms with 1 to 4 heteroatoms.

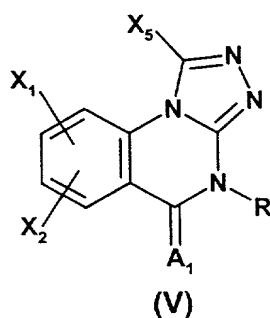
- In particular manner for the groups  $X_1$  and  $X_2$  :

$X_1$  and  $X_2$  are particularly localized in position 6 and 7 of the main quinazolinone cycle.

- In particular manner for the groups  $R_4$  and  $R_5$  :

$R_4$  and  $R_5$  are lower alkyl,  $R_4$  and  $R_5$  being able to be linked to form a saturated cycle or including one or several double-bonds with one or several heteroatoms chosen among O, S or N, substituted by one or several groups chosen among hydroxy, keto, lower alkyl or lower alkoxy. The particularly preferred substituents forming the group  $NR_4R_5$  includes pyrrolidine, 3-hydroxy pyrrolidine, thiamorpholine, dimethyl amino, azepanyl and piperidinyl.

A third series of intermediaries includes the following general formula V compounds:



in which  $X_1$ ,  $X_2$ ,  $X_5$ ,  $A_1$  and R are such as previously defined.

For the groups as above, the following substituents are particularly preferred :

- In a general manner for the groups  $X_1$ ,  $X_2$  and  $X_5$  :

- halogen : F, Cl, Br, I, preferably Br and Cl,

- lower alkyl : linear or branched comprising from 1 to 6, preferably 1 to 3 carbon atoms,

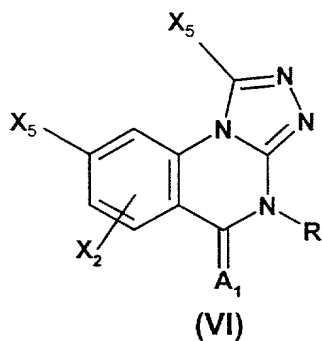
- lower alkoxy : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms:

- In particular manner for the groups  $X_1$  and  $X_2$  :

$X_1$  and  $X_2$  are particularly localized in position 6 and 7 of the main quinazolinone cycle.

5 - In particular manner for the group  $X_5$  :  $X_5$  is F, Br or Cl.

A fourth series of intermediaries includes the following general formula VI compounds :



in which  $X_2$ ,  $X_5$ ,  $A_1$  and R are such as previously defined.

10 For the groups as above, the following substituents are particularly preferred :

- In a general manner for the groups  $X_2$  and  $X_5$  :

- halogen : F, Cl, Br, I, preferably Br and Cl,

- lower alkyl : linear or branched comprising from 1 to 6, preferably 1 to 3 carbon  
15 atoms ,

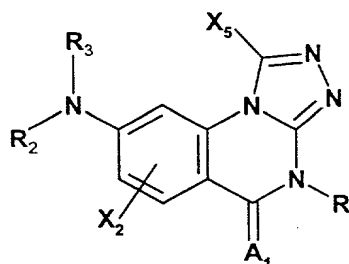
- lower alkoxy : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon  
atoms .

- In particular manner for the group  $X_2$  :

20  $X_2$  is particularly localized in position 7 of the main quinazolinone cycle.

- In particular manner for the group  $X_5$  :  $X_5$  is F, Br or Cl.

A fifth series of intermediaries includes the following general formula VII compounds :



in which  $X_2$ ,  $X_5$ ,  $A_1$ ,  $R_2$ ,  $R_3$  are such as previously defined.

For the groups as above, the following substituents are particularly preferred :

- In a general manner for the groups  $X_2$ ,  $X_5$ ,  $R_2$  and  $R_3$  :

- 5 - halogen : F, Cl, Br, I, preferably Br and Cl,
- lower alkyl : linear or branched comprising from 1 to 6, preferably 1 to 3 carbon atoms ,
- lower alkoxy : linear or branched comprising from 1 to 5, preferably 1 to 3 carbon atoms ,
- 10 - hydrogen, lower alkyl, possibly substituted by one or several groups hydroxy, halogen, cyano, lower alkoxy or  $-CO-Q_1-Q_2-Q_3$ ,  $R_2$  and  $R_3$  being able to be linked to form a cycle, including one or several heteroatoms chosen among O, S or N and possibly bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy or  $-CO-Q_1-Q_2-Q_3$ .

- In particular manner for the group  $X_2$  :

$X_2$  is particularly localized in position 7 of the main quinazolinone cycle.

- In particular manner for the group  $X_5$  :  $X_5$  is F, Br or Cl.

- In particular manner for the groups  $R_2$  and  $R_3$  :

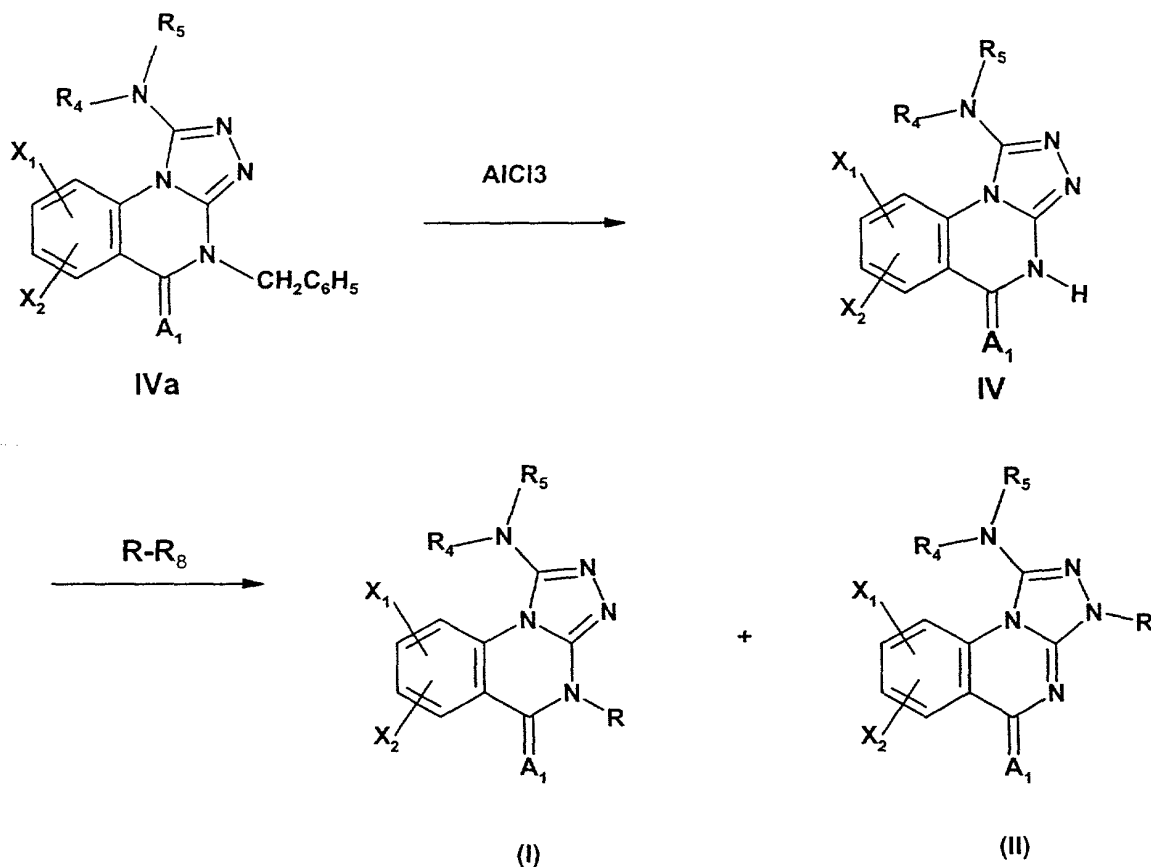
$R_2$  and  $R_3$ , similar or different, are hydrogen, lower alkyl  $R_2$  and  $R_3$  being able to be linked to form a cycle, including one or several heteroatoms chosen among O, S or N and possibly substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy or  $CO-Q_1-Q_2-Q_3$ . Among the particular preferred embodiments of the substituent  $NR_2R_3$ , we find the groups azepanyl, pyrrolidine,  $NH_2$  and  $NHCH_3$ .

### **Synthesis processes of formula I and II compounds**

- 30 A) The compounds of the current invention can be obtained by bringing several synthesis processes into operation. Some of these synthesis processes are disclosed below.

The compounds of the current invention can be initially obtained in a convergent manner by the method represented in scheme 1.

# SCHEME 1



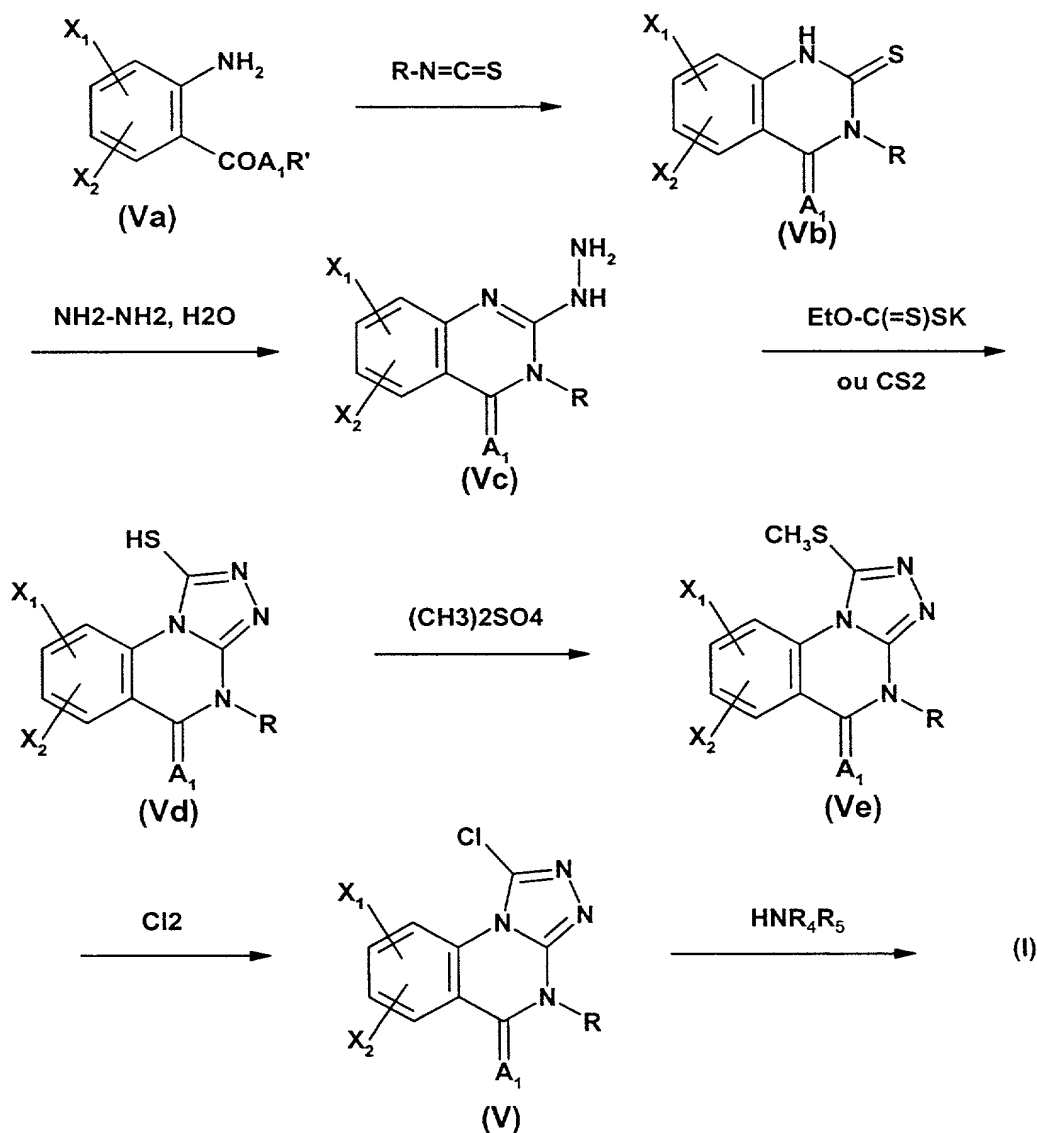
in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R$ ,  $R_4$  and  $R_5$  are such as previously defined, and  $R_8$  represents  $Cl$ ,  $Br$ ,  $OSO_2CH_3$ ,  $OSO_2CF_3$  or  $OSO_2Ar$ .

- 10 The 4-benzyl 1-amino triazolo [4,3-a] quinazoline-5-one and/or -5-thione (IVa) is treated by aluminium trichloride in aromatic solvent such as benzene or toluene to make the corresponding compound N-debenzylated (IV). This one is therefore treated in basic conditions by a halide or a sulfonate chosen according to desired substituent  $R$ ; for example sodium hydride in a solvent such as 1, 2-dimethoxyethane (DME) or cesium in
- 15 dimethylformamide, to lead to 1-amino triazolo [4,3-a] quinazoline-5-ones of formula (I) and (II).

In fact, relying of the basic conditions used, the alkylation is a little regioselective in some cases. Then we obtain a mixture of N<sub>4</sub> and N<sub>3</sub>, regioisomers, (I) and (II) respectively. The two compounds are usually separated by conventional chromatographic methods.

- 5 **B)** Another example of synthesis method used to construct correctly substituted formula (I) triazolo [4,3-a] quinazoline-5-one and/or -5-thione motif is illustrated by scheme 2 :

SCHEME 2



in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R$ ,  $R_4$  and  $R_5$  are such as previously defined and,

R' represents a linear or branched lower alkyl group comprising from 1 to 6, preferably 1 to 3 carbon atoms.

5 An acid or anthranilic ester which is correctly substituted on the aromatic cycle (Va) is initially transformed into corresponding 2-thio quinazoline-4-one and/or -4-thione (Vb) by cyclization using isothiocyanate of alkyl, aryl or aralkyl, in a solvent such as acetic acid or pyridine.

10 The thio quinazoline-4-one and/or -4-thione (Vb) is treated by hydrazine hydrate to give 2-hydrazino quinazoline-4-one and/or -4-thione (Vc) which is also cyclized into 1-mercapto triazolo [4,3-a] quinazoline-5-one and/or -5-thione (Vd) by action of potassium xanthogenate or other reagents such as CS<sub>2</sub>.

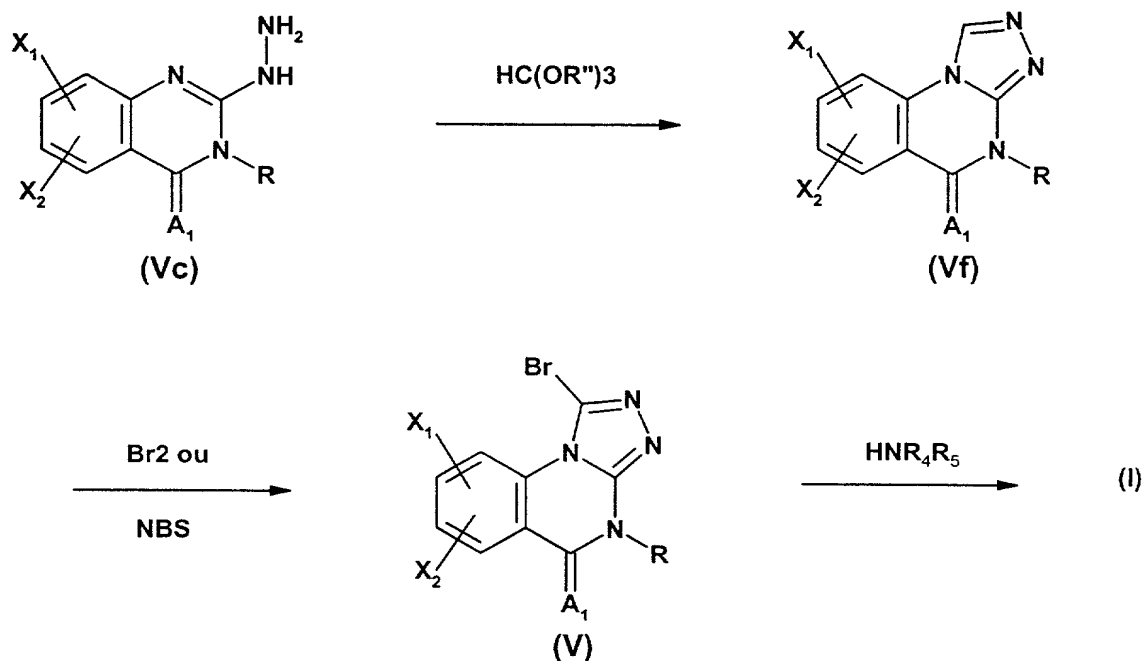
By action of an alkylating agent such as dimethyl sulfate, the thiol (VI) is transformed into derivative 1-methylthio (Ve) which is then converted using chlorine, into 1-chloro triazolo [4,3-a] quinazoline-5-one and/or -5-thione (V).

15 This latter is treated by a primary or secondary amine to lead finally to 1-amino triazolo [4,3-a] quinazoline-5-one of formula (I).

C) Another advantageous method in some cases is represented in scheme 3.

20

### SCHEME 3



in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R$ ,  $R_4$  and  $R_5$  are such as previously defined and,

- 5  $R''$  represents a linear or branched lower alkyl group comprising from 1 to 6, preferably 1 to 3 carbon atoms such as  $\text{CH}_3$  or  $\text{C}_2\text{H}_5$ .

La 2-hydrazino quinazoline-4-one and/or -4-thione (Vc), obtained from an anthranilate in 2 steps (as illustrated in scheme 2), is cyclized using alkyl orthoformate, in acid medium, into triazolo [4,3-a] quinazoline-5-one and/or -5-thione (Vf).

This is then brominated by bromine or N-bromosuccinimide (NBS) to give 1-bromotriazolo [4,3-a] quinazoline-5-one and/or -5-thione (V).

This brominated derivative is finally treated by ethanolic solution of primary or secondary amine to lead to formula (I) 1-amino triazolo [4,3-a] quinazoline-5-one and/or -5-thione.

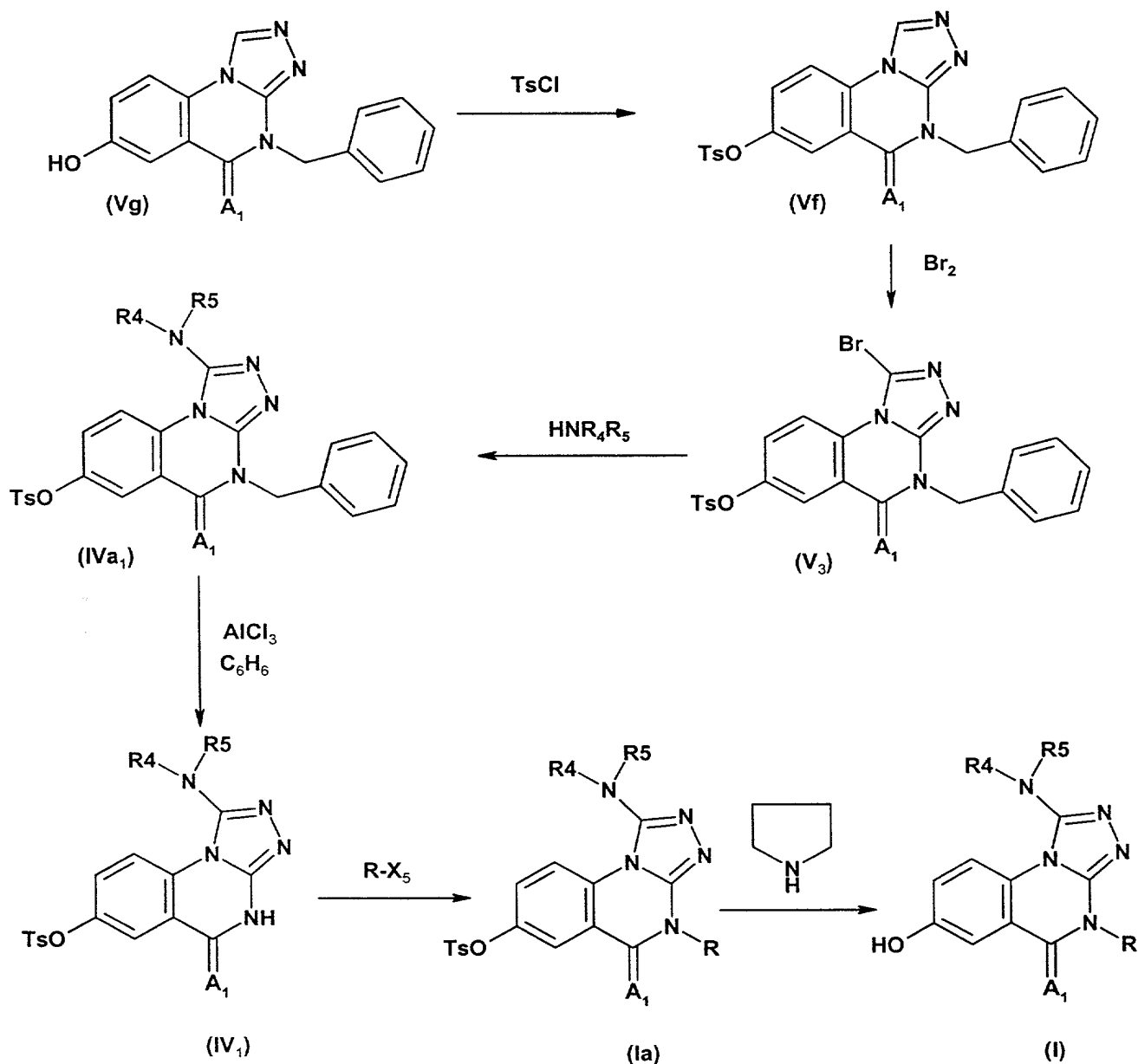
15 D) When  $X_1$  represents H and  $X_2$  represent a reactive phenolic function OH, this group must generally be protected during the last steps of compound (I) synthesis. As an example, scheme 4 shows synthesis of such as hydroxylated in position 7 compound. The 4-benzyl-7-hydroxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (Vg), obtained by a method represented in scheme 3, is treated by a compound allowing insertion of oxygen protector group (P) on the function OH. The person skilled in the art will be able to choose without any

problem the appropriate protector group. The protector group can be chosen also among silyl trimethyl, methoxymethyl, tolylsulfonyl, methylsulfonyl (mesyl) or also methoxyethylmethoxy (MEM). As an example, the compound (Vg) is treated by tosyl chloride, in a solvent such as methylene chloride, in the presence of a base or an amine such as triethylamine, to give the corresponding O-tosyled phenol (Vf). This is treated by bromine to lead to 4-benzyl-1-bromo-7-(4-tolylsulfonyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (V<sub>3</sub>), which reacts with an amine HNR<sub>4</sub>R<sub>5</sub> by reflux, preferably in the presence of a base like sodium bicarbonate, in a solvent such as dimethylformamide, to give the 1-amino-4-benzyl-7-(4-tolylsulfonyl) -4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (IVa<sub>1</sub>).

We can then replace the benzyl group in position 4 by another group R, for example by debenzylating the compound (IVa<sub>1</sub>) obtained previously using aluminium chloride in a solvent like benzene, then by alkylating the obtained intermediate (IV<sub>1</sub>) by treatment with a halide or a sulfonate R-X<sub>s</sub>, in basic conditions, to obtain the 1-amino-7-(4-tolylsulfonyl) -4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (Ia) diversely substituted in position 4. These ones are preferably detosyled into 7-hydroxy derivative (I) for example by heating for several hours in pyrrolidine.



SCHEMA 4



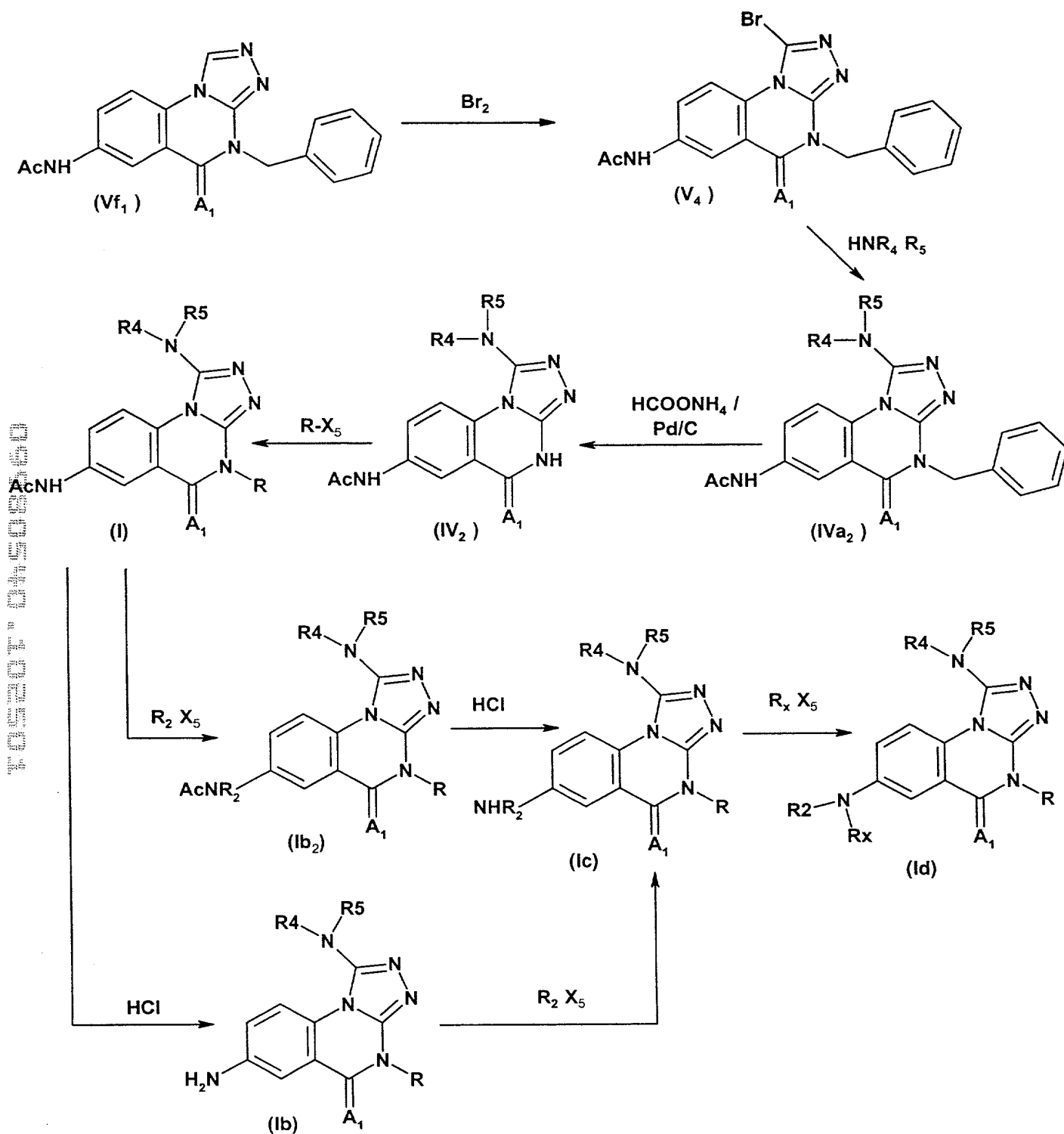
In which  $\text{A}_1$ ,  $\text{R}_4$  and  $\text{R}_5$  are such as previously defined.

E) When  $\text{X}_1$  represents H and  $\text{X}_2$  represents a reactive anilino function  $\text{NH}_2$ ,  $\text{NHR}_2$  or  $\text{NR}_2\text{R}_x$  ( $\text{R}_2$  such as previously defined and  $\text{R}_x$  represents  $\text{R}_2$  or such as previously defined), the amino group  $\text{NH}_2$  must generally be protected during the last steps of the compound (I) synthesis. As an example, scheme 5 shows synthesis of such as aminated compound in position 7. The 7-acetamido-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (Vf<sub>1</sub>), obtained by a method represented in scheme 3, is treated by bromine to lead to

the 7-acétamido-4-benzyl-1-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (V<sub>4</sub>). This one is used in the reaction with an amine HNR<sub>4</sub>R<sub>5</sub> by reflux, preferably in the presence of a base as sodium bicarbonate, in a solvent such as dimethylformamide, to give the 7-acétamido-1-amino-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (IV<sub>a2</sub>). In the example disclosed above, the protector group (P<sub>1</sub>) of the function NH is an acetyl group. However the man of art may choose another protector group, for example methylsulfonyl, tolylsulfonyl or phtalimido.

We can also replace the benzyl group in position 4 by another group R, for example by debenzylating the compound (IV<sub>a2</sub>) obtained previously, using ammonium formate and palladium on charcoal, in a solvent such as tetrahydrofuran, then by alkylating the obtained intermediate (IV<sub>2</sub>) by treatment with a halide or a sulfonate R-X<sub>5</sub>, in basic conditions, to obtain the 7-acetamido-1-amino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (I) diversely substituted in position 4. These ones can be N-deacetylated into final compounds (Ib) bearing a function NH<sub>2</sub> in position 7, by classic methods like for example by reflux heating in an aqueous solution of hydrochloric acid. The compounds can be treated in at their turn, relying on the case, by a reagent R<sub>2</sub>-X<sub>5</sub> (R<sub>2</sub> and X<sub>5</sub> having the meaning given previously) to lead to a final N-monosubstituted compound (Ic), which then can be treated by a reagent R<sub>x</sub>X<sub>5</sub> to lead to a final N,N-disubstituted compound (Id). Also it is possible to treat 7-acetamido-1-amino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one and/or -5-thione (I) diversely substituted in position 4 initially by a reagent R<sub>2</sub>X<sub>5</sub> to obtain (1b<sub>2</sub>) which is then N-deacetylated to obtain the compound (Ic).

SCHEMA 5

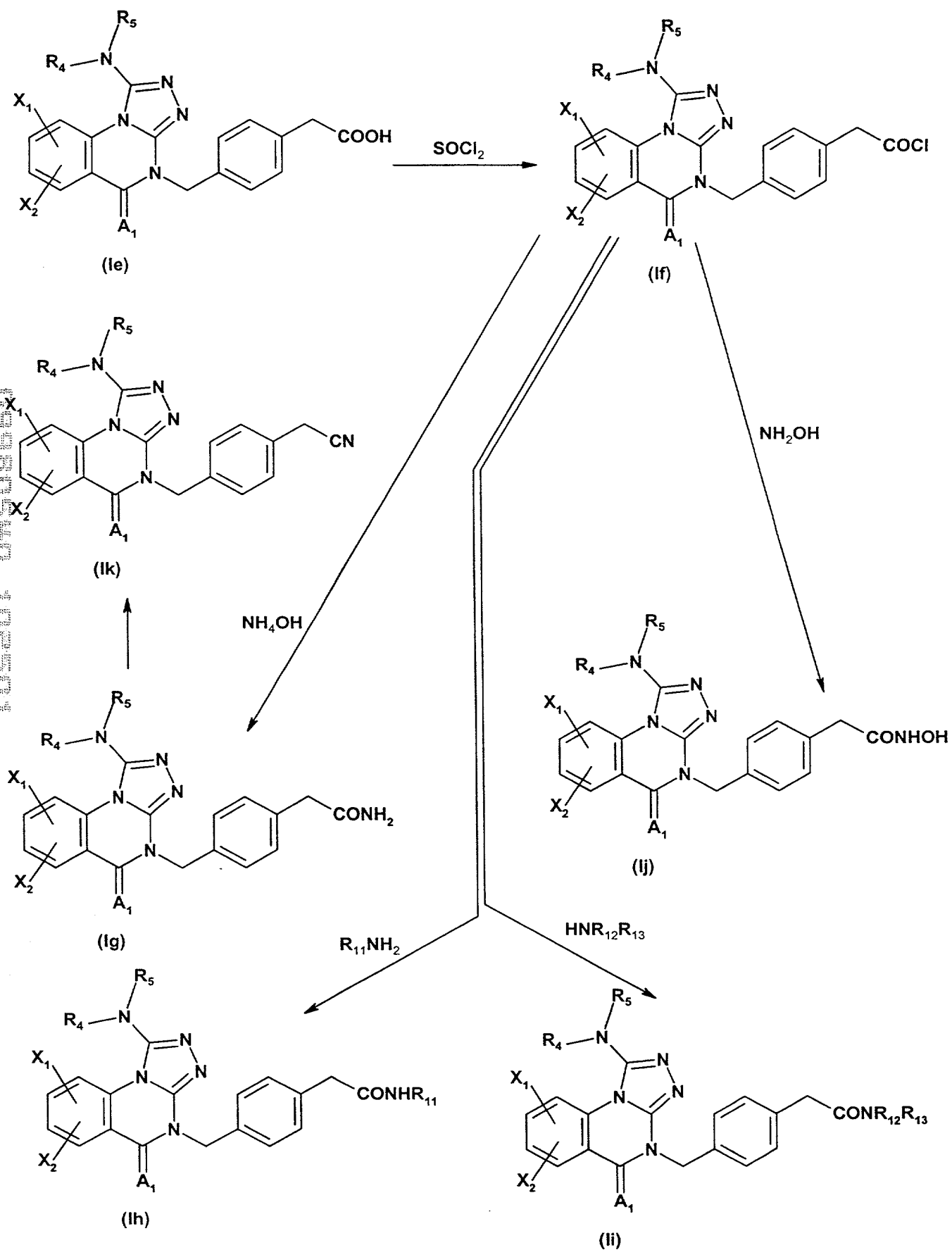


F) When the substituent R in position 4 of compounds (I) represents a group 4-(carboxymethyl)-benzyl, it can be advantageous to transform the carboxylic acid function into

ester, amide, nitrile or hydroxamic acid derived. For that, methods represented in scheme 6 can be applied to a general formula acid (Id). This is transformed into chloride of acid (Ie), which is directly condensed either with ammonia to give a primary amide (If), either with a primary or secondary amine to give a secondary (Ih) or tertiary (Ii) amide respectively. (In these structures,  $R_{11}$  has the same meaning as  $R_2$  and  $R_{12}$  have the same meaning as  $R_4$ ,  $R_5$  respectively).

The hydroxamic acid (Ij) can be obtained by reaction of chloride of acid (Ie) with hydroxylamine. The primary amide (If) can be dehydrated by classic and current methods, for example using phosphorus pentoxide to lead to corresponding nitrile (Ig).

SCHEMA 6

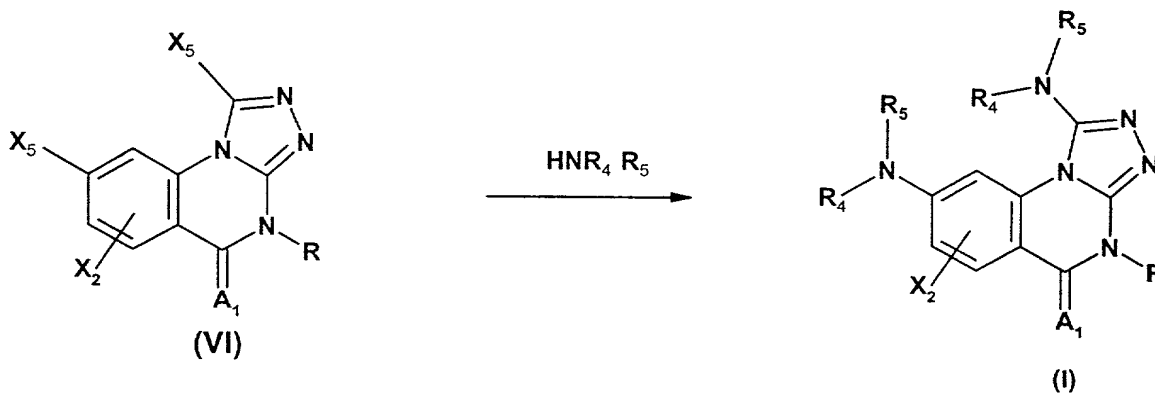


In which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are such as previously defined.

5 **G)** The compounds of structure (I) in which  $X_1$  or  $X_2$  represents an amino  $NR_2R_3$  group in position 8 identical to the  $NR_4R_5$  group, can also be obtained by heating of corresponding 1-bromo (VI ;  $X_5 = \text{hal}$ ) intermediates in the presence of an excess of  $HNR_4R_5$  amine, without solvent or in a solvent such as dimethylformamide as illustrated in scheme 7.

#### SCHEME 7

10



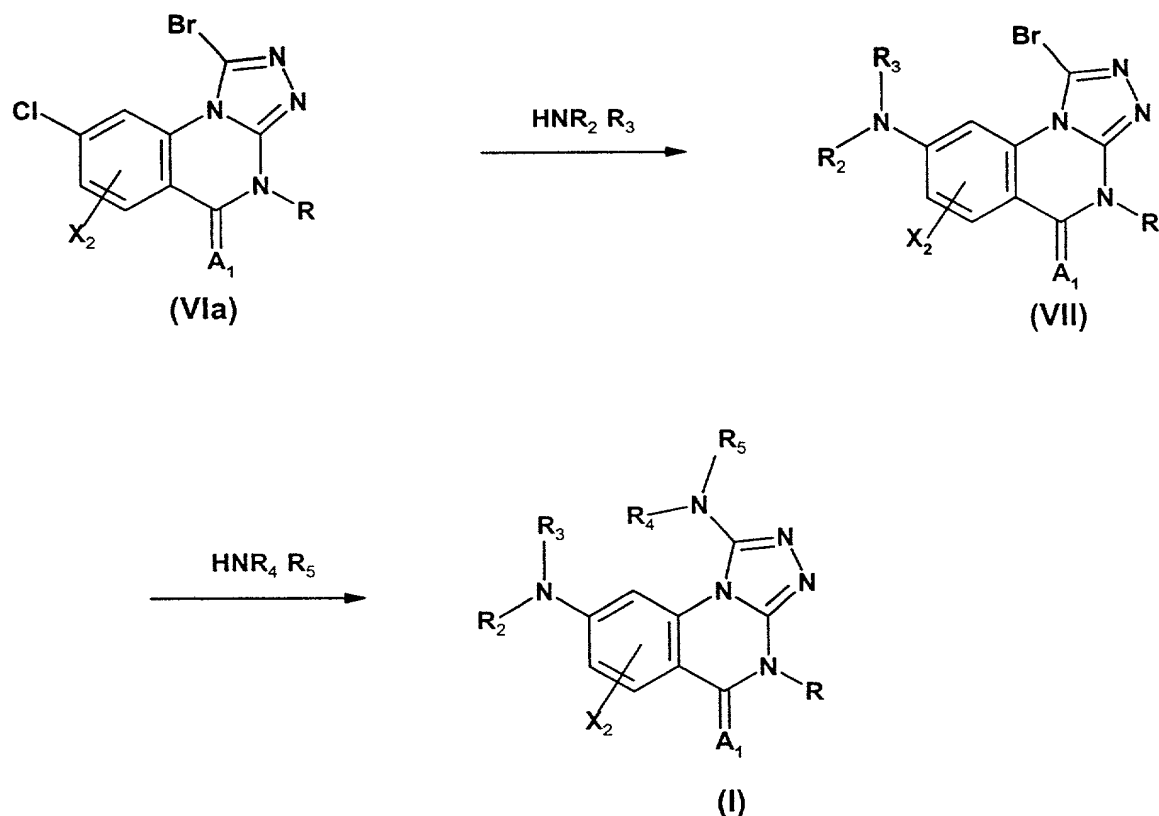
in  $X_2$ ,  $X_5$ ,  $A_1$ ,  $R$ ,  $R_4$  and  $R_5$  are such as previously defined.

15 However it is preferable to avoid for this reaction type substituents  $R$  including a halogen group able to react in a competitive manner with the reagent  $HNR_4R_5$ .

**H)** In the case where two  $NR_2R_3$  and  $NR_4R_5$  amino groups are different, a slightly modified synthesis path is indicated in scheme 8.

#### SCHEME 8

20



in which  $X_2$ ,  $A_1$ ,  $R$ ,  $R_2$ ,  $R_3$ ,  $R_4$  and  $R_5$  are such as previously defined. The substituent amino  $\text{NR}_2\text{R}_3$  is localized in position 8.

1-bromo 8-chlorotriazolo [4,3-a] quinazoline-5-one and/or -5-thione (VIa) correctly substituted in position 4, and prepared as previously by bromination of non-substituted in position 1 derivative, is treated by slight excess of amine  $\text{HNR}_2\text{R}_3$ , in a solvent such as dimethylformamide to lead to intermediate (VII).

This intermediate is also heated in an excess of amine  $\text{HNR}_4\text{R}_5$ , in a solvent such as dimethylformamide to lead to compound (I).

Surprisingly, the inventors have noticed that reactivity of the halogen atom in position 8 is much more important than reactivity of the other halogen atom of the intermediate. This allows then a first selective reaction on the level of this halogen in position 8 than can be followed by reaction on the level of the second halogen. The example as above illustrates use of chlorine in position 8. However it is possible to use other halogens such as bromine and fluorine, the latter proving to be particularly reactive.

## Examples

### A. Type (I) and (II) compounds

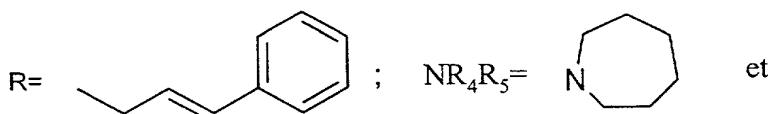
#### Examples 1 and 2

**METHOD A :** 1-Azepanyl-7-chloro-4-(3-phénylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (ex. 1)

(I):  $X_1 = 7 - \text{Cl}$  ;  $X_2 = \text{H}$  ;

1-Azepanyl-7-chloro-3-(3-phénylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (ex. 2)

(II) :  $X_1 = 7 - \text{Cl}$  ;  $X_2 = \text{H}$  ;



In a reactor protected from humidity, we place 2.5 g (7.87 mmol) of 1-Azepan-yl-7-chloro-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one, in suspension in 35 ml of 1,2-dimethoxyethane then we shake.

Under inert atmosphere, we then add 240 mg of sodium hydride suspension at 75 % (representing 7.90 mmol NaH).

The mixture is heated to 60° C under shaking for 6 hours.

Then we add 1.56 g (7.90 mmol) of cinnamyl bromide by fraction.

The obtained mixture is heated then to 60° C for 20 hours, under shaking.

After cooling down, the suspension is poured into 200 ml of iced water.

We extract three times with ethyl acetate; the joined organic phases are washed with aqueous solution saturated with sodium chloride, dried on sodium sulfate; then the solvent is evaporated under vacuum.

We obtain 3.5 g of crude mixture of the two regioisomers (theory : 3.4 g).

The 2 isomers are separated by flash chromatography on silica column with elution using methylene chloride 99 / methanol 1 mixture.

In order of elution we obtain,:



1) 0.58 g of compound from example 1

Yield = 17 %

F (Tottoli) = 125°C

CCM (CH<sub>2</sub> Cl<sub>2</sub> 98 / CH<sub>3</sub> OH 2) = 0.60

5 RMN<sup>1</sup> H δ (ppm) CDCl<sub>3</sub> : 1.7 – 2.0 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.45 (dt, 1H) ; 6.9

(d, 1H) ; 7.15 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H).

2) 2.1 g of compound from example 2

Yield = 61.5 %

10 F (Tottoli) = 188°C

CCM (CH<sub>2</sub> Cl<sub>2</sub> 98 / CH<sub>3</sub> OH 2) : R<sub>f</sub> = 0.35.

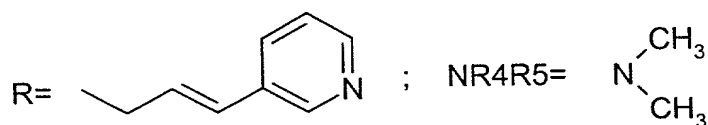
RMN<sup>1</sup> H δ (ppm) CDCl<sub>3</sub> :

1.7 – 2.0 (m, 8H) ; 3.4 (m, 4H) ; 4.9 (d, 2H) ; 6.35 (d, 1H) ; 6.75 (d, 1H) ; 7.2 – 7.45 (m, 5H) ; 7.65 (d, 1H) ; 8.2 (d, 1H) ; 8.45 (s, 1H)

15 **Example 3 :**

**METHOD**            **B :**            7-bromo-1-(N,N-dimethylamino)-4-[3-(3-pyridyl)-allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (ex. 3)

(I): X<sub>1</sub> = 7 – Br ; X<sub>2</sub> = H ;



In a reactor equipped with magnetic shaker and refrigeration, we resuspend 7.4 g (0.024 mol) of 7-bromo-1-(N,N-dimethylamino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one in 200 ml de  
25 1,2-dimethoxyethane then we shake. We add 17.0g (0.052mol) of cesium carbonate then shake at ambient temperature for 15 minutes. 4.5g (0.024mol) of 3-(3-pyridyl)-allyl chloride hydrochloride are then added by fraction, then the mixture is heated to 70°C, under shaking, for 3 hours. The solvent is evaporated under vacuum then the residue is then put in suspension in 300 ml of iced water. After repeated extractions with ethyl acetate, the joined organic  
30 phases are washed with aqueous solution saturated with sodium chloride, dried on sodium sulfate then the solvent is evaporated under vacuum.

The residue is chromatographed on silica column by elution using CH<sub>2</sub>Cl<sub>2</sub> 98 / CH<sub>3</sub>OH 2 / NH<sub>4</sub>OH 0,2 mixture. We recover 6.3g of isomer (I) pure in CCM. This one is recrystallized in 20ml of isopropanol to give 5.3g of example 3 compound:

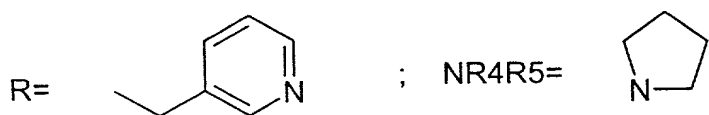
Yield = 52%

- 5 RMN<sup>1</sup> H  $\delta$  (ppm) CDCl<sub>3</sub> : 2.95 (s, 6H) ; 5.1 (d, 2H) ; 6.45 (dt, 1H) ; 6.8 (d, 1H) ; 7.15 (m, 1H) ; 7.65 (d, 1H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.4 – 8.6 (m, 3H).

#### Examples 4 and 5 :

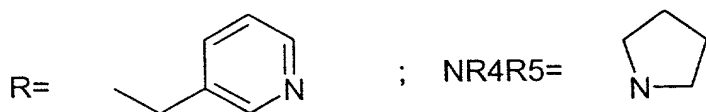
**METHOD C :** 7-bromo-1-(pyrrolidin-1-yl)-4-[(3-pyridyl)-methyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (ex. 4)

- 10 (I): X<sub>1</sub> = 7 – Br ; X<sub>2</sub> = H ;



7-bromo-1-(pyrrolidin-1-yl)-3-[(3-pyridyl)-methyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (ex. 5)

(II) : X<sub>1</sub> = 7-Br ; X<sub>2</sub> = H ;



15

- In a reactor protected from humidity, equipped with magnetic shaking and refrigeration, we add 2.0g (0.006 mol) of 1-(pyrrolidin-1-yl)-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one into 125 ml of dimethylsulfoxide (DMSO) solution then we add 1.0g (0.018 mol) of finely crushed potash. The mixture is shaken at ambient temperature for 1.5 h, until obtaining of slightly cloudy solution. Then we add once 0.82g (0.005 mol) of 3-picolyl chloride hydrochloride then keep shaking at ambient temperature for 4 hours.

- The obtained mixture is poured into iced water and the resulting suspension is extracted 3 times with ethyl acetate. The joined organic extracts are washed in NaCl saturated solution, dried on Na<sub>2</sub>SO<sub>4</sub> then concentrated under vacuum. We obtain 2.0g of crude mixture of the 2 regioisomers which are separated by chromatography on silica column by elution using CH<sub>2</sub>Cl<sub>2</sub> 98 - CH<sub>3</sub>OH 2 - NH<sub>4</sub>OH 0.4 mixture.

In elution order we obtain:

1) 1.2g of majority product which is recrystallized in methanol to give after drying under vacuum 1,1g of example 4 compound.

Yield = 57 %

F (Tottoli) = 206-207°C

5 CCM (CH<sub>2</sub> Cl<sub>2</sub> 97 / CH<sub>3</sub> OH 3 / NH<sub>4</sub>OH 0.3) : Rf = 0.30

RMN<sup>1</sup> H δ (ppm) CDCl<sub>3</sub> : 1.95 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.2 – 7.3 (dd, 1H) ; 7.85 (d, 1H) ; 8.0 (d, 1H) ; 8.2 (d, 1H) ; 8.45 – 8.55 (m, 2H) ; 8.9 (s, 1H).

2) 0.25g of minority product which is recrystallized in methanol to give after drying under vacuum 0.17g of example 5 compound .

Yield = 12%

F (Tottoli) = 261-262°C

CCM (CH<sub>2</sub> Cl<sub>2</sub> 97 / CH<sub>3</sub> OH 3 / NH<sub>4</sub>OH 0.3) : Rf = 0.20













15 RMN<sup>1</sup> H δ (ppm) CDCl<sub>3</sub> : 1.9 – 2.05 (m, 4H) ; 3.2 – 3.4 (m, 4H) ; 5.25 (s, 2H) ; 7.1 – 7.2 (m, 1H) ; 7.7 (d, 1H) ; 7.8 (d, 1H) ; 7.9 (d, 1H) ; 8.45 – 8.60 (m, 2H) ; 8.65 (s, 1H).

Compounds (I) of examples 6 to 108 and compounds (II) of examples 109 to 162, in which X<sub>2</sub> = H<sub>1</sub> are prepared according to process of example 1 :



















Compounds (I) : Table 1





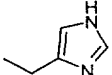

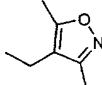

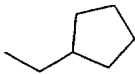





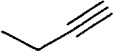







## Compounds (II) : Table 2












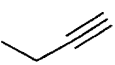







TABLE 1

N <sub>o</sub> . Compound	X1	R	NR <sub>4</sub> R <sub>5</sub>	Yield (%)	MP (°C)	Method
6	H	(E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		11	144	A
7	7-Cl	CH <sub>2</sub> =CHCH <sub>2</sub>		9	-	A
8	7-Cl	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		16	163	A
9	7-Cl	2-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		6	160-162	A
10	7-Cl	3-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		35	157	A
11	7-Cl	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		20	166	A
12	7-Cl	4-BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		25	104-110	A
13	7-Cl	4-FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		48	150	A
14	7-Cl	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		22	138	A
15	7-Cl	4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		49	165-168	A
16	7-Cl	2-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		6	98-100	A
17	7-Cl	3-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		22	138	A
18	7-Cl	4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		26	138	A
19	7-Cl	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>		19	-	A
20	7-Cl	3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>		41	172	A
21	7-Cl	(2-pyridyl)CH <sub>2</sub>		16	152	A
22	7-Cl	(3-pyridyl)CH <sub>2</sub>		29	155	A















N <sub>o</sub> . Compound	X1	R	NR <sub>4</sub> R <sub>5</sub>	Yield (%)	MP (°C)	Method
23	7-Cl	(4-pyridyl)CH <sub>2</sub>		64	137	A
24	7-Cl	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>		5	105	A
25	7-Cl	4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>2</sub>		12	136	A
26	7-Cl	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>3</sub>		17	-	A
27	7-Cl	C <sub>6</sub> H <sub>5</sub> C(=O)CH <sub>2</sub>		26,5	105-107	A
28	7-Cl	4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> C(=O)CH <sub>2</sub>		30	191	A
29	7-Cl	4-ClC <sub>6</sub> H <sub>4</sub> C(=O)CH <sub>2</sub>		36	190	A
30	7-Cl	4-(CH <sub>3</sub> O)-3-(COOCH <sub>3</sub> )-C <sub>6</sub> H <sub>3</sub> C(=O)CH <sub>2</sub>		18	140	A
31	7-Cl	(3-pyridyl)-CH <sub>2</sub>		39	176	C
32	7-Br	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		8	179	A
33	7-Br	4-FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		21	158	A
34	7-Br	4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		21	190	A
35	7-Br	3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>		23,5	185	A
36	7-Br	(3-pyridyl)-CH <sub>2</sub>		4	180	C
37	7-Br	(E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		64	155	B
38	7-Br	(E) 4-Cl-C <sub>6</sub> H <sub>4</sub> CH=CHCH <sub>2</sub>		25	176	B
39	7-Br	(E) 4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> CH=CHCH <sub>2</sub>		30	129	B
40	7-Br	(E) (3-pyridyl)CH=CHCH <sub>2</sub>		12	185	B

N <sup>o</sup> . Compound	X1	R	NR <sub>4</sub> R <sub>5</sub>	Yield (%)	MP (°C)	Method
41	7-Br	(E) (4-pyridyl)CH=CHCH <sub>2</sub>		39	216	B
42	7-Br	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		53	215	B
43	7-Br	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		12	105	A
44	7-Br	4-FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		42	166	A
45	7-Br	3-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		52	206	B
46	7-Br	4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		19	116	A
47	7-Br	4-(COOCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		54	205	A
48	7-Br	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		52	200	B
49	7-Br	4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		39	169	B
50	7-Br	4-(OCOCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		21	195	B
51	7-Br	4-OHC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		13	288	B
52	7-Br	3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>		15	151	A
53	7-Br	3,4-(OCH <sub>2</sub> O)C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>		21	194	A
54	7-Br	3,5-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>		31	-	A
55	7-Br	3,4,5-(CH <sub>3</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> CH <sub>2</sub>		35	141-143	A
56	7-Br	4-(CH <sub>2</sub> COOH)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		17	260	B
57	7-Br	(E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		57	152-155	A
58	7-Br	(Z) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		24	110	B

N <sub>o</sub> . Compound	X1	R	NR <sub>4</sub> R <sub>5</sub>	Yield (%)	MP (°C)	Method
59.	7-Br	(E) (4-ClC <sub>6</sub> H <sub>4</sub> )- CH=CHCH <sub>2</sub>		45	187	B
60	7-Br	(E) (4- CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> CH=CHCH <sub>2</sub>		32	171	B
61	7-Br	(E) (3-pyridyl)- CH=CHCH <sub>2</sub>		10	102	B
62	7-Br	(E) (4-pyridyl)- CH=CHCH <sub>2</sub>		38	167	B
63	7-Br			4	290(dec)	B
64	7-Br			60	221	B
65	7-Br			32	155	B
66	7-Br	n-butyl		39	135	B
67	7-Br	CH <sub>2</sub> CF <sub>3</sub>		14	202	B
68	7-Br	CH <sub>2</sub> CH <sub>2</sub> OH		25	240	B
69	7-Br	CH <sub>2</sub> CH <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>		50	215 (HCl)	C
70	7-Br			36	204	B
71	7-Br	CH <sub>2</sub> CH <sub>2</sub> OC <sub>6</sub> H <sub>5</sub>		25	171	B
72	7-Br	CH <sub>2</sub> CH <sub>2</sub> SC <sub>6</sub> H <sub>5</sub>		20	122	B
73	7-Br	CH(C <sub>6</sub> H <sub>5</sub> )COOCH <sub>3</sub>		14	184	B
74	7-Br	4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		72	200	B
75	7-Br	3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>		67	178	B
76	7-Br	(E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		8	-	A

N <sub>o</sub> . Compound	X1	R	NR <sub>4</sub> R <sub>5</sub>	Yield (%)	MP (°C)	Method
77	7-Br	(E) (3-pyridyl)CH=CHCH <sub>2</sub>		48	177	B
78	7-Br	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		56	223	B
79	7-Br	4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		56	207	B
80	7-Br	4-OHC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		15	284	B
81	7-Br	4-(COOCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		35	197	B
82	7-Br	4-(CH <sub>2</sub> COOH)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		8	246	B
83	7-Br	4-(CH <sub>2</sub> CN)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		<1	230	B
84	7-Br	(3-pyridyl)-CH <sub>2</sub>		28	142	B
85	7-Br	(E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		63	171	B
86	7-Br	(Z) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		28	167	B
87	7-Br	(E) (4-pyridyl)-CH=CHCH <sub>2</sub>		48	115	B
88	7-Br			<1	234	B
89	7-Br	C <sub>6</sub> H <sub>5</sub> C=CCH <sub>2</sub>		15	159	B
90	7-Br	CH(C <sub>6</sub> H <sub>5</sub> )COOCH <sub>3</sub>		18	243	B
91	7-CH <sub>3</sub>	(3-pyridyl)-CH <sub>2</sub>		64	175	C
92	7-CH <sub>3</sub>	(E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		16	195	A
93	7-CH <sub>3</sub>	4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		84	166	B
94	7-CH <sub>3</sub>	3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>		52	184	B



N <sup>o</sup> . Compound	X1	R	NR <sub>4</sub> R <sub>5</sub>	Yield (%)	MP (°C)	Method
95	7-CH <sub>3</sub>	4-(COOCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		44	230	B
96	7-CH <sub>3</sub>	4-(CH <sub>2</sub> COOH)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		21	262	B
97	7-CH <sub>3</sub>	(3-pyridyl)-CH <sub>2</sub>		10	139	C
98	7-CH <sub>3</sub>	(E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		17	173	A
99	7-CH <sub>3</sub>	4-(CH <sub>2</sub> COOH)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		10	-	B
100	7-CH <sub>3</sub>	(E) (3-pyridyl)CH=CHCH <sub>2</sub>		51	230	B
101	7-CH <sub>3</sub>	4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		73	201	B
102	7-CH <sub>3</sub>	4-(CH <sub>2</sub> COOH)C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		3	-	B
103	7-CH <sub>3</sub>	(E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		50	171	B
104	7-CH <sub>3</sub>	(E) (3-pyridyl)CH=CHCH <sub>2</sub>		53	155	B
105	7-CH <sub>3</sub>	(E) (4-pyridyl)-CH=CHCH <sub>2</sub>		66	119	B
106	8-CH <sub>3</sub>	(E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		52	-	A
107	7-CN	4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		43	147-149	B
108	7-OH	(E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		3	295(dec)	A

**- Compound 6 :**

R.M.N. <sup>1</sup>H δ (ppm) : 1.7 – 1.85 (m, 8H) ; 3.3 – 3.4 (m, 4H) ; 4.95 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.7 – 6.75 (d, 1H) ; 7.25 (t, 1H) ; 7.3 (t, 2H) ; 7.45 (d, 2H) ; 7.6 (t, 1H) ; 7.95 (t, 1H) ; 8.25 (d, 1H) ; 8.4 (d, 1H)

Solvent : DMSO

**- Compound 7 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.5 – 1.9 (m, 8H) ; 3.3 (m, 4H) ; 4.8 (d, 2H) ; 5.2 (d, 1H) ; 5.4 (d, 1H) ; 5.95 (m, 1H) ; 7.65 (d, 1H) ; 8.25 (s, 1H) ; 8.3 (d, 1H)

Solvent : CDCl<sub>3</sub>

5

**- Compound 8 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.7 – 2.0 (m, 8H) ; 2.3 (s, 3H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.1 (d, 2H) ; 7.6 (d, 2H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent : CDCl<sub>3</sub>

10

**- Compound 9 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.6 (s, 2H) ; 7.05 – 7.25 (m, 3H) ; 7.4 (d, 1H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.45 (d, 1H)

Solvent : CDCl<sub>3</sub>

15

**- Compound 10 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.6 – 2.0 (m, 8H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.2 (m, 2H) ; 7.55 (s, 1H) ; 7.65 (s, 1H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent : CDCl<sub>3</sub>

20

**- Compound 11 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.65 – 1.9 (m, 8H) ; 3.3 (m, 4H) ; 5.35 (s, 2H) ; 7.2 (d, 2H) ; 7.55 (d, 2H) ; 7.65 (d, 1H) ; 8.25 (m, 2H)

Solvent : CDCl<sub>3</sub>

25

**- Compound 12 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1,7 – 2 (m, 8H) ; 3,4 (m, 4H) ; 5,4 (s, 2H) ; 7,4 (d, 2H) ; 7,55 (d, 2H) ; 7,7 (d, 1H) ; 8,3 (s, 1H) ; 8,35 (d, 1H)

Solvent : CDCl<sub>3</sub>

30

**- Compound 13 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.4 (s, 2H) ; 7.0 (m, 2H) ; 7.7 (m, 3H) ; 8.35 (m, 2H)

Solvent :  $\text{CDCl}_3$

**- Compound 14 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.5 (s, 2H) ; 7.55 (d, 2H) ; 7.7 (d, 1H) ;  
5 7.8 (d, 2H) ; 8.3 – 8.45 (m, 2H)

Solvent :  $\text{CDCl}_3$

**- Compound 15 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.65 – 2 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.55 (d, 2H) ; 7.7 – 7.85 (m,  
10 3H) ; 8.25 – 8.45 (m, 2H)

Solvent :  $\text{CDCl}_3$

**- Compound 16 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.5 (s, 2H) ; 6.8 (t, 1H) ;  
15 6.9 (d, 1H) ; 7.1 (d, 1H) ; 7.2 (t, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 17 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.8 (s, 3H) ; 5.5 (s, 2H) ; 6.8 (m, 1H) ;  
20 7.25 (m, 3H) ; 7.75 (d, 1H) ; 8.4 (m, 2H)

Solvent :  $\text{CDCl}_3$

**- Compound 18 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.75 (s, 3H) ; 5.4 (s, 2H) ; 6.85 (d,  
25 2H) ; 7.7 (m, 3H) ; 8.35 (m, 2H)

Solvent :  $\text{CDCl}_3$

**- Compound 19 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 2.0 (m, 8H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.3 (d, 1H) ; 7.5 (d, 1H) ;  
30 7.75 (m, 2H) ; 8.3 (s, 1H) ; 8.35 (d, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 20 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.85 (s, 3H) ; 3.90 (s, 3H) ; 5.4 (s, 2H) ; 6.75 (d, 1H) ; 7.35 (m, 2H) ; 7.7 (d, 1H) ; 8.35 (m, 2H)

Solvent : CDCl<sub>3</sub>

**- Compound 21 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.6 (s, 2H) ; 7.15 (m, 1H) ; 7.4 (d, 1H) ; 7.6 (m, 1H) ; 7.75 (d, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H) ; 8.45 (m, 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 22 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.6 – 1.95 (m, 8H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.2 (m, 1H) ; 7.7 (d, 1H) ; 8.0 (m, 1H) ; 8.3 (m, 2H) ; 8.5 (m, 1H) ; 8.9 (s, 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 23 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.6 – 1.9 (m, 8H) ; 3.3 (m, 4H) ; 5.35 (s, 2H) ; 7.4 (d, 2H) ; 7.65 (d, 1H) ; 8.25 (s, 1H) ; 8.3 (d, 1H) ; 8.45 (d, 2H)

Solvent : CDCl<sub>3</sub>

**- Compound 24 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.7 – 2.1 (m, 8H) ; 3.15 (t, 2H) ; 3.4 (m, 4H) ; 4.5 (t, 2H) ; 7.2-7.45 (m, 5H) ; 7.7 (d, 1H) ; 8.35 (s, 1H) ; 8.35 (s, 1H) ; 8.4 (d, 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 25 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.05 (t, 2H) ; 3.4 (m, 4H) ; 3.8 (s, 3H) ; 4.45 (t, 2H) ; 6.85 (d, 2H) ; 7.25 (d, 2H) ; 7.7 (d, 1H) ; 8.3 (s, 1H) ; 8.4 (d, 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 26 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.7 – 2.0 (m, 8H) ; 2.2 (qn, 2H) ; 2.75 (t, 2H) ; 3.35 (m, 4H) ; 4.35 (t, 2H) ; 7.0 – 7.2 (m, 5H) ; 7.7 (d, 1H) ; 8.3 (s, 1H) ; 8.35 (d, 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 27 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.65-1.85(m,8H) ; 3.35(m,4H) ; 5.7(s,2H) ; 7.6(t,2H) ; 7.75(t,1H) ;

5 8.05(d,1H) ; 8.15(m,3H) ; 8.4(d,1H)

Solvent : DMSO

**- Compound 28 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 5.7 (s, 2H) ; 7.0 (d, 2H) ;

10 7.8 (d, 1H) ; 8.05 (d, 2H) ; 8.35 (s, 1H) ; 8.45 (d, 1 H)

Solvent : CDCl<sub>3</sub>

**- Compound 29 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.7 (s, 2H) ; 7.45 (d, 2H) ; 7.8 (d,

15 1H) ; 8 (d, 2H) ; 8.3 (s, 1H) ; 8.4 (d, 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 30 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.75 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 3.9 (s, 3H) ; 4 (s, 3H) ; 5.7 (s, 2H) ;

20 7.1 (d, 1H) ; 7.8 (d, 1H) ; 8.2 (d, 1 H) ; 8.35 (s, 1H) ; 8.45 (s, 1H) ; 8.5 (s, 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 31 :**

R.M.N.<sup>1</sup>H δ (ppm) : 2.0 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.2 - 7.3 (dd, 1H) ;

25 7.75 (d, 1H) ; 8.05 (d, 1H) ; 8.25 (d, 1H) ; 8.35 (s, 1 H) ; 8.55 (d, 1H) ; 8.9 (s, 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 32 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.25 (d, 2H) ; 7.75 (d,

30 2H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.45 (s, 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 33 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.7 – 2.0 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 6.9 – 7.0 (m, 2H) ;

35 7.65 - 7.75 (m, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 34 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.8 – 2 (m, 8H) ; 3.35 – 3.5 (m, 4H) ; 5.5 (s, 2H) ; 7.6 (dd, 2H) ; 7.8  
5 (dd, 2H) ; 7.9 (m, 1H) ; 8.3 (dd, 1H) ; 8.5 (d, 1H)

Solvent :  $\text{CHCl}_3$

**- Compound 35 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 3.8 (s, 3H) ; 3.85 (s, 3H) ; 5.4 (s,  
10 2H) ; 6.8 (d, 1H) ; 7.25 – 7.35 (m, 2H) ; 7.8 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 36 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.8 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.45 (s, 2H) ; 7.25 (m, 1H) ; 7.9 (d,  
15 1H) ; 8.1 (d, 1H) ; 8.35 (d, 1H) ; 8.5 (m, 2H) ; 8.95 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 37 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.95 (m, 8H) ; 3.4 (m, 4H) ; 5.05 (d, 2H) ; 6.45 (dt, 1H) ; 6.9 (d,  
20 1H) ; 7.15 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 38 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.35 – 6.45 (m, 1H) ;  
25 6.75 – 6.85 (d, 1H) ; 7.2 – 7.35 (m, 4H) ; 7.85 (m, 1H) ; 8.3 (m, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 39 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.95 (m, 8H) ; 3.3 – 3.45 (m, 4H) ; 3.75 (s, 3H) ; 5.05 (m, 2H) ;  
30 6.25 – 6.35 (m, 1H) ; 6.8 (m, 3H) ; 7.3 (m, 2H) ; 7.85 (m, 1H) ; 8.3 (m, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 40 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.45 – 6.55 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.65 (m, 1H) ; 7.9 (m, 1H) ; 8.35 (d, 1H) ; 8.45 (m, 1H) ; 8.5 (d, 1H) ; 8.6 (d, 1H)

5 Solvent :  $\text{CDCl}_3$

**- Compound 41 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 2 (m, 8H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (d, 2H) ; 6.55 – 6.7 (m, 1H) ; 6.8 (d, 1H) ; 7.2 (d, 2H) ; 7.9 (m, 1H) ; 8.3 (d, 1H) ; 8.5 (m, 3H)

10 Solvent :  $\text{CDCl}_3$

**- Compound 42 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 - 2.1 (m, 4H) ; 2.3 (s, 3H) ; 3.3 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 7.1 (d, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.5 (s, 1H)

15 Solvent :  $\text{CDCl}_3$

**- Compound 43 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.9 – 2.05 (m, 4H) ; 3.25 – 3.4 (m, 4H) ; 5.35 (s, 2H) ; 7.2 (d, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.4 (s, 1H)

20 Solvent :  $\text{CDCl}_3$

**- Compound 44 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.0 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 5.4 (s, 2H) ; 6.9 – 7.0 (m, 2H) ; 7.6 – 7.7 (m, 2H) ; 7.85 (d, 1H) ; 8.1 (d, 1H) ; 8.5 (s, 1H)

25 Solvent :  $\text{CDCl}_3$

**- Compound 45 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.45 (s, 2H) ; 7.45 (t, 1H) ; 7.55 (d, 1H) ; 7.85 – 8.0 (m, 3H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

30 Solvent :  $\text{CDCl}_3$

**- Compound 46 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.95 – 2.1 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.45 (s, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 2H) ; 7.9 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 47 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 3.9 (s, 3H) ; 5.5 (s, 2H) ; 7.7 (d, 2H) ; 7.9 (d, 1H) ; 8.0 (d, 2H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 48 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.15 (m, 4H) ; 3.3 – 3.45 (m, 4H) ; 5.5 (s, 2H) ; 7.75 – 7.9 (m, 3H) ; 8.1 – 8.2 (m, 3H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 49 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 3.75 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 2H) ; 7.65 (d, 2H) ; 7.8 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 50 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.15 (m, 4H) ; 2.25 (s, 3H) ; 3.35 – 3.45 (m, 4H) ; 5.45 (s, 2H) ; 7.0 (d, 2H) ; 7.75 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 51 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.9 – 2.1 (m, 4H) ; 3.2 – 3.45 (m, 4H) ; 5.2 (s, 2H) ; 6.7 (d, 2H) ; 7.35 (d, 2H) ; 8 (d, 1H) ; 8.2 (d, 1H) ; 8.3 (s, 1H) ; 9.25 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 52 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.0 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 3.85 (s, 3H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.2 – 7.35 (m, 2H) ; 7.8 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)



Solvent :  $\text{CDCl}_3$

**- Compound 53 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.0 – 2.1 (m, 4H) ; 3.3 – 3.4 (m, 4H) ; 5.35 (s, 2H) ; 5.9 (s, 2H) ; 6.7 (d,  
5 1H) ; 7.15 – 7.3 (m, 2H) ; 7.85 (d, 1H) ; 8.1 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**Compound 54 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.1 (m, 4H) ; 3.35 – 3.4 (m, 4H) ; 3.75 (s, 6H) ; 5.4 (s, 2H) ; 6.35 (s,  
10 1H) ; 6.8 (s, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 55 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.1 (m, 4H) ; 3.35 – 3.45 (m, 4H) ; 3.8 (s, 3H) ; 3.85 (s, 6H) ; 5.4 (s,  
15 2H) ; 7 (s, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 56 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.95 – 2.1 (m, 4H) ; 3.25 – 3.45 (m, 4H) ; 3.55 (s, 2H) ; 5.4 (s, 2H) ; 7.25  
20 (d, 2H) ; 7.35 (d, 2H) ; 8.15 (d, 1H) ; 8.2 (d, 1H) ; 8.35 (s, 1H) ; 12.2 – 12.5 (m, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 57 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 5.05 (d, 2H) ; 6.4 (dt, 1H) ; 6.9 (d, 1H) ; 7.15  
25 – 7.3 (m, 3H) ; 7.35 (d, 2H) ; 7.9 (d, 1H) ; 8.15 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 58 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.0 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.2 (d, 2H) ; 5.7 – 5.8 (m, 1H) ;  
30 6.7 (d, 1H) ; 7.2 – 7.45 (m, 5H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.6 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 59 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.05 (m, 4H) ; 3.4 (m, 4H) ; 5 (d, 2H) ; 6.4 (m, 1H) ; 6.85 (d, 1H) ; 7.15 – 7.3 (m, 4H) ; 7.85 (m, 1H) ; 8.15 (d, 1H) ; 8.45 (s, 1H)

Solvent :  $\text{CDCl}_3$

5

**- Compound 60 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.95 – 2.10 (m, 4H) ; 3.4 (m, 4H) ; 3.75 (s, 3H) ; 4.95 (m, 2H) ; 6.25 – 6.35 (m, 1H) ; 6.75 – 6.9 (m, 3H) ; 7.2 – 7.3 (m, 2H) ; 7.85 (m, 1H) ; 8.15 (m, 1H) ; 8.45 (m, 1H)

Solvent :  $\text{CDCl}_3$

10

**- Compound 61 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.95 – 2.15 (m, 4H) ; 3.3 – 3.5 (m, 4H) ; 5.05 (m, 2H) ; 6.45 – 6.55 (m, 1H) ; 6.75 – 6.9 (d, 1H) ; 7.2 (m, 1H) ; 7.6 – 7.7 (m, 1H) ; 7.85 – 7.95 (m, 1H) ; 8.15 (m, 1H) ; 8.4 (m, 1H) ; 8.5 (m, 1H) ; 8.6 (m, 1H)

Solvent :  $\text{CDCl}_3$

15

**- Compound 62 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.9 – 2.05 (m, 4H) ; 3.3 – 3.45 (m, 4H) ; 5.05 (d, 2H) ; 6.55 – 6.7 (m, 1H) ; 6.8 (d, 1H) ; 7.25 (m, 2H) ; 7.9 (m, 1H) ; 8.2 (m, 1H) ; 8.45 - 8.55 (m, 3H)

Solvent :  $\text{CDCl}_3$

20

**- Compound 63 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.8 – 1.9 (m, 2H) ; 3.25 (m, 2H) ; 5.1 (s, 2H) ; 6.9 (s, 1H) ; 7.4 (s, 1H) ; 8 (d, 1H) ; 8.1 (d, 1H) ; 8.2 (s, 1H) ; 11.8 (m, 1H)

Solvent : DMSO

25

**- Compound 64 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.05 – 2.15 (m, 4H) ; 2.4 (s, 3H) ; 2.6 (s, 3H) ; 3.4 (m, 4H) ; 5.2 (s, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.4 (s, 1H)

Solvent :  $\text{CDCl}_3$

30

**- Compound 65 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.25 – 1.75 (m, 8H) ; 1.9 – 2.05 (m, 4H) ; 2.5 – 2.7 (m, 1H) ; 3.3 – 3.4 (m, 4H) ; 4.2 (d, 2H) ; 7.8 (d, 1H) ; 8.1 (d, 1H) ; 8.45 (s, 1H)

Solvent :  $\text{CDCl}_3$

5

**- Compound 66 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1 (t, 3H) ; 1.4 – 1.55 (m, 2H) ; 1.8 – 1.9 (m, 2H) ; 2.0 – 2.1 (m, 4H) ; 3.4 – 3.5 (m, 4H) ; 4.3 (t, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

10

**- Compound 67 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.15 (m, 4H) ; 3.35 – 3.5 (m, 4H) ; 5.0 (q, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.55 (s, 1H)

Solvent :  $\text{CDCl}_3$

15

**- Compound 68 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 (m, 4H) ; 3.15 (m, 1H) ; 3.3 (m, 4H) ; 4.05 (m, 2H) ; 4.5 (m, 2H) ; 7.08 (m, 1H) ; 8.15 (m, 1H) ; 8.4 (s, 1H)

Solvent :  $\text{CDCl}_3$

20

**- Compound 69 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.1 (t, 6H) ; 2.0 – 2.1 (m, 4H) ; 2.65 (q, 4H) ; 2.9 (t, 2H) ; 3.35 – 3.45 (m, 4H) ; 4.4 (t, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

25

**- Compound 70 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.15 (m, 4H) ; 2.3 (s, 1H) ; 3.35 – 3.5 (m, 4H) ; 5.1 (s, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

30

**- Compound 71 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.1 (m, 4H) ; 3.4 (m, 4H) ; 4.45 (m, 2H) ; 4.75 (m, 2H) ; 6.9 (m, 3H) ; 7.2 – 7.3 (m, 2H) ; 7.9 (m, 1H) ; 8.2 (m, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 72 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.1 (m, 4H) ; 3.45 (m, 6H) ; 4.6 (m, 2H) ; 7.1 (m, 1H) ; 7.2 (m, 2H) ; 7.4 (m, 2H) ; 7.85 (m, 1H) ; 8.1 (m, 1H) ; 8.45 (s, 1H)

5 Solvent :  $\text{CDCl}_3$

**- Compound 73 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.9 - 2.05 (m, 4H) ; 3.3 - 3.4 (m, 4H) ; 3.08 (s, 3H) ; 6.7 (s, 1H) ; 7.2 - 7.35 (m, 3H) ; 7.7 - 7.85 (m, 3H) ; 8.1 (d, 1H) ; 8.4 (s, 1H)

10 Solvent :  $\text{CDCl}_3$

**- Compound 74 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.4 - 1.6 (m, 1H) ; 1.7 - 2 (m, 5H) ; 3 - 3.1 (m, 2H) ; 3.3 - 3.4 (m, 2H) ; 5.5 (s, 2H) ; 7.6 (d, 2H) ; 7.8 (d, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.5 (s, 1H)

15 Solvent :  $\text{CDCl}_3$

**- Compound 75 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.4 (m, 1H) ; 1.7 - 1.95 (m, 5H) ; 3 - 3.1 (m, 2H) ; 3.3 - 3.4 (m, 2H) ; 3.8 (s, 3H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.25 - 7.35 (m, 2H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.40 (s, 1H)

20

Solvent :  $\text{CDCl}_3$

**- Compound 76 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.35 - 2.1 (m, 6H) ; 3.05 (t, 2H) ; 3.35 (m, 2H) ; 5.1 (d, 2H) ; 6.5 (dt, 1H) ; 6.9 (d, 1H) ; 7.1 - 7.5 (m, 5H) ; 7.9 (d, 1H) ; 8.3 (d, 1H) ; 8.55 (s, 1H)

25

Solvent :  $\text{CDCl}_3$

**- Compound 77 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.9 (m, 4H) ; 3.45 (m, 2H) ; 3.6 (m, 2H) ; 5.1 (m, 2H) ; 6.5 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.65 (m, 1H) ; 7.9 (m, 1H) ; 8.25 (m, 1H) ; 8.45 (m, 1H) ; 8.5 (m, 1H) ; 8.55 (s, 1H)

30

Solvent :  $\text{CDCl}_3$

**- Compound 78 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.3 (s, 3H) ; 2.9 (s, 6H) ; 5.4 (s, 2H) ; 7.1 (d, 2H) ; 7.6 (d, 2H) ; 7.85 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

5

**- Compound 79 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.95 (s, 6H) ; 5.45 (s, 2H) ; 7.55 (d, 2H) ; 7.75 (d, 2H) ; 7.9 (d, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

10

**- Compound 80 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.85 (s, 6H) ; 5.2 (s, 2H) ; 6.7 (d, 2H) ; 7.3 (d, 2H) ; 8 (d, 1H) ; 8.2 – 8.3 (m, 2H) ; 9.3 (s, 1H)

Solvent :  $\text{CDCl}_3$

15

**- Compound 81 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.9 (s, 6H) ; 3.9 (s, 3H) ; 5.45 (s, 2H) ; 7.7 (m, 2H) ; 7.85 (m, 1H) ; 7.9 (m, 2H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

20

**- Compound 82 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.85 (s, 6H) ; 3.6 (s, 2H) ; 5.35 (s, 2H) ; 7.25 (d, 2H) ; 7.5 (d, 2H) ; 8.15 (d, 1H) ; 8.3 (d, 1H) ; 8.35 (s, 1H) ; 12.2 – 12.45 (m, 1H)

Solvent : DMSO

25

**- Compound 83 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.9 (s, 6H) ; 3.7 (s, 2H) ; 5.45 (s, 2H) ; 7.25 (m, 2H) ; 7.7 (m, 2H) ; 7.85 (m, 1H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

Solvent :  $\text{CDCl}_3$

30

**- Compound 84 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.9 (s, 6H) ; 5.5 (s, 2H) ; 7.25 (m, 1H) ; 7.85 (m, 1H) ; 8.05 (m, 1H) ; 8.25 (d, 1H) ; 8.5 (m, 2H) ; 8.9 (s, 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 85 :**

R.M.N.<sup>1</sup>H δ (ppm) : 2.9 (s, 6H) ; 5.05 (d, 2H) ; 6.4 – 6.55 (dt, 1H) ; 6.9 (d, 1H) ; 7.2 – 7.4 (m, 5H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.55 (s, 1H)

5 Solvent : CDCl<sub>3</sub>

**- Compound 86 :**

R.M.N.<sup>1</sup>H δ (ppm) : 2.95 (s, 6H) ; 5.29 (d, 2H) ; 5.7 – 5.8 (m, 1H) ; 6.7 (d, 1H) ; 7.2 – 7.45 (m, 5H) ; 7.9 (d, 1H) ; 8.25 (d, 1H) ; 8.5 (s, 1H)

10 Solvent : CDCl<sub>3</sub>

**- Compound 87 :**

R.M.N.<sup>1</sup>H δ (ppm) : 2.9 (s, 6H) ; 5.05 (d, 2H) ; 6.55 – 6.7 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 2H) ; 7.85 (m, 1H) ; 8.25 (d, 1H) ; 8.5 (m, 3H)

15 Solvent : CDCl<sub>3</sub>

**- Compound 88 :**

R.M.N.<sup>1</sup>H δ (ppm) : 2.8 (s, 6H) ; 3.2 (s, 1H) ; 4.9 (s, 2H) ; 8.1 (m, 1H) ; 8.2 (d, 1H) ; 8.3 (s, 1H)

20 Solvent : DMSO

**- Compound 89 :**

R.M.N.<sup>1</sup>H δ (ppm) : 2.9 (s, 6H) ; 5.2 (s, 2H) ; 7.2 (m, 3H) ; 7.4 (m, 2H) ; 7.85 (m, 1H) ; 8.2 (d, 1H) ; 8.55 (s, 1H)

25 Solvent : CDCl<sub>3</sub>

**- Compound 90 :**

R.M.N.<sup>1</sup>H δ (ppm) : 2.95 (s, 6H) ; 3.85 (s, 3H) ; 6.8 (s, 1H) ; 7.3 – 7.4 (m, 3H) ; 7.75 – 7.9 (m, 3H) ; 8.2 (d, 1H) ; 8.5 (s, 1H)

30 Solvent : CDCl<sub>3</sub>

**- Compound 91 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.75 – 1.9 (m, 8H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 5.5 (s, 2H) ; 7.2 – 7.3 (dd, 1H) ; 7.6 – 7.65 (d, 1H) ; 8.05 – 8.01 (d, 1H) ; 8.2 (s, 1H) ; 8.3 – 8.35 (d, 1H) ; 8.55 (d, 1H) ; 8.95 (s, 1H)

5 Solvent :  $\text{CDCl}_3$

**- Compound 92 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.75 – 2 (m, 8H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 5.1 (d, 1H) ; 5.4 – 5.55 (dt, 1H) ; 6.9 – 7 (d, 1H) ; 7.2 – 7.3 (m, 4H) ; 7.4 (d, 2H) ; 7.6 (d, 1H) ; 8.2 (s, 1H) ; 8.3 (d, 1H)

10

Solvent :  $\text{CDCl}_3$

**- Compound 93 :**

15 R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.1 (m, 4H) ; 2.5 (s, 3H) ; 3.3 – 3.4 (m, 4H) ; 5.5 (s, 2H) ; 7.6 (m, 3H) ; 7.8 (d, 2H) ; 8.1 – 8.2 (m, 2H)

Solvent :  $\text{CDCl}_3$

**- Compound 94 :**

20 R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.1 (m, 4H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 3.8 (s, 3H) ; 3.9 (s, 3H) ; 5.4 (s, 2H) ; 6.8 (d, 1H) ; 7.3 – 7.4 (m, 2H) ; 7.5 (d, 1H) ; 8.1 – 8.2 (m, 2H)

Solvent :  $\text{CDCl}_3$

25 **- Compound 95 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.1 – 2.2 (m, 4H) ; 2.5 (s, 3H) ; 3.4 – 3.5 (m, 4H) ; 3.9 (s, 3H) ; 5.5 (s, 2H) ; 7.6 (m, 1H) ; 7.7 (m, 2H) ; 7.95 – 8 (m, 2H) ; 8.1 – 8.2 (m, 2H)

Solvent :  $\text{CDCl}_3$

30 **- Compound 96 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2 (m, 4H) ; 2.5 (s, 3H) ; 3.3 – 3.4 (m, 4H) ; 3.6 (s, 2H) ; 5.3 (s, 2H) ; 7.3 (m, 2H) ; 7.45 (m, 2H) ; 7.8 (m, 2H) ; 8.1 (s, 1H) ; 8.2 (d, 2H) ; 12.4 (m, 1H)

Solvent : DMSO

**- Compound 97 :**

R.M.N.<sup>1</sup>H δ (ppm) : 1.95 (m, 4H) ; 2.5 (s, 3H) ; 3.35 (m, 4H) ; 5.4 (s, 2H) ; 7.35 (dd, 1H) ; 7.55 (d, 1H) ; 8.05 (s, 1H) ; 8.15 (d, 1H) ; 8.5 (d, 1H) ; 8.7 (s, 1H)

Solvent : DMSO

5

**- Compound 98 :**

R.M.N.<sup>1</sup>H δ (ppm) : 2 – 2.1 (m, 4H) ; 2.45 (s, 3H) ; 3.3 – 3.45 (m, 4H) ; 5.05 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.85 – 6.95 (d, 1H) ; 7.1 – 7.45 (m, 5H) ; 7.6 (d, 1H) ; 8.1 – 8.2 (m, 2H)

Solvent : CDCl<sub>3</sub>

10

**- Compound 99 :**

R.M.N.<sup>1</sup>H δ (ppm) : 2.4 – 3.75 (m, 13H) ; 5.35 (s, 2H) ; 7.1 – 7.5 (m, 4H) ; 7.8 (d, 1H) ; 8.1 (s, 1H) ; 8.25 (d, 1H)

Solvent : DMSO

15

**- Compound 100 :**

R.M.N.<sup>1</sup>H δ (ppm) : 2.5 (s, 3H) ; 2.9 (m, 4H) ; 3.45 (m, 2H) ; 3.65 (m, 2H) ; 5.1 (m, 2H) ; 6.5 (m, 1H) ; 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.6 (m, 1H) ; 7.7 (m, 1H) ; 8.2 (m, 2H) ; 8.45 (d, 1H) ; 8.6 (1s, 1H)

20 Solvent : CDCl<sub>3</sub>

**- Compound 101 :**

R.M.N.<sup>1</sup>H δ (ppm) : 2.5 (s, 3H) ; 2.95 (s, 6H) ; 5.5 (s, 2H) ; 7.6 (m, 3H) ; 7.8 (m, 2H) ; 8.15 – 8.25 (m, 2H)

25 Solvent : CDCl<sub>3</sub>

**- Compound 102 :**

R.M.N.<sup>1</sup>H δ (ppm) : 2.2 (s, 3H) ; 2.6 (s, 6H) ; 3.25 (s, 2H) ; 5.1 (s, 2H) ; 7 (m, 2H) ; 7.15 (m, 2H) ; 7.5 (m, 1H) ; 7.8 (s, 1H) ; 8 (d, 1H) ; 12 (m, 1H)

30 Solvent : DMSO



**- Compound 103 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.5 (s, 3H) ; 3 (s, 6H) ; 5.1 (d, 2H) ; 6.4 – 6.5 (dt, 1H) ; 6.9 (d, 1H) ; 7.15 – 7.4 (m, 6H) ; 7.6 (d, 1H) ; 8.2 (m, 1H)

Solvent :  $\text{CDCl}_3$

5

**- Compound 104 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.5 (s, 3H) ; 2.95 (s, 6H) ; 5.1 (d, 2H) ; 6.45 – 6.55 (dt, 1H) ; 6.8 – 6.85 (d, 1H) ; 7.2 (m, 1H) ; 7.6 (dd, 1H) ; 7.7 (dd, 1H) ; 8.2 – 8.25 (m, 2H) ; 8.4 (d, 1H) ; 8.6 (s, 1H)

10 Solvent :  $\text{CDCl}_3$

**- Compound 105 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.5 (s, 3H) ; 2.95 (s, 6H) ; 5.1 (d, 2H) ; 6.6 – 6.7 (dt, 1H) ; 6.8 (d, 1H) ; 7.2 (d, 2H) ; 7.6 (d, 1H) ; 8.2 – 8.25 (dd, 2H) ; 8.5 (d, 2H)

15 Solvent :  $\text{CDCl}_3$

**- Compound 106 :**

R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 2 (m, 8H) ; 2.55 (m, 3H) ; 3.35 – 3.6 (m, 4H) ; 5.1 (d, 2H) ; 6.45 (dt, 1H) ; 6.85 (d, 1H) ; 7.1 – 7.45 (m, 6H) ; 8.25 (m, 2H)

20 Solvent :  $\text{CDCl}_3$

**- Compound 107 :** R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 2.9 (d, 6H) ; 5.5 (s, 2H) ; 7.6 (m, 2H) ; 7.7 (m, 2H) ; 8.0 (m, 1H) ; 8.4 (m, 1H) ; 8.7 (s, 1H)

Solvent :  $\text{CDCl}_3$
















25

**- Compound 108 :**










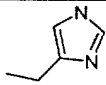








R.M.N.  $^1\text{H}$   $\delta$  (ppm) : 1.9 (m, 4H) ; 3.25 (m, 4H) ; 6.85 (d, 2H) ; 6.3 – 6.4 (dt, 1H) ; 6.6 – 6.7 (d, 1H) ; 7.15 – 7.3 (m, 4H) ; 7.35 – 7.4 (d, 2H) ; 7.5 (s, 1H) ; 8.05 (d, 1H) ; 10.1 (m, 1H),





Solvent : DMSO

TABLE 2

N° Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
109	H	(E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		28	176	A
110	7-Cl	CH <sub>2</sub> =CHCH <sub>2</sub>		24	173	A
111	7-Cl	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		58	148	A
112	7-Cl	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		50	182	A
113	7-Cl	2-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		77	228	A
114	7-Cl	3-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		31	166	A
115	7-Cl	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		60	245	A
116	7-Cl	4-BrC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		38	244	A
117	7-Cl	4-FC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		42,5	224	A
118	7-Cl	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		39	232	A
119	7-Cl	4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		46	> 260	A
120	7-Cl	2-(OCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		57	184	A
121	7-Cl	3-(OCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		46	163	A
122	7-Cl	4-(OCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		32,5	164-165	A
123	7-Cl	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>		60	212	A

Nº Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
124	7-Cl	3,4-(OCH3)2C6H3CH2		39	153	A
125	7-Cl	(2-pyridyl)CH2		9	153	A
126	7-Cl	(3-pyridyl)CH2		8	184	C
127	7-Cl	C6H5CH2CH2		7	196	A
128	7-Cl	4(CH3O)C6H4(CH2)2		61	196	A
129	7-Cl	C6H5(CH2)3		36	130	A
130	7-Cl	C6H5C(=O)CH2		38,5	230-232	A
131	7-Cl	4(CH3O)C6H4C(=O)CH2		42	238	A
132	7-Cl	4-ClC6H4C(=O)CH2		59	238	A
133	7-Cl	4(CH3O)-3-(COOCH3)-C6H3C(=O)CH2		30	136	A
134	7-Br	4-ClC6H4CH2		57	247	A
135	7-Br	4-FC6H4CH2		54	216	A
136	7-Br	4-CNC6H4CH2		53	293	A
137	7-Br	3,4-(CH3O)2C6H3CH2		61	174	A
138	7-Br	4-(CH2COOH)C6H4CH2		1	269	B
139	7-Br	(3-pyridyl)CH2		4	192	C
140	7-Br	(E) C6H5CH=CHCH2		70	198	A
141	7-Br	(Z) C6H5CH=CHCH2		57	187	A
142	7-Br	4-ClC6H4CH2		18	185	A

N° Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
143	7-Br	4-FC6H4CH2		16	233	A
144	7-Br	4-CNC6H4CH2		52	222	A
145	7-Br	4-(COOCH3)C6H4CH2		31	193	A
146	7-Br	4-(CH3O)C6H4CH2		14	164	B
147	7-Br	4-(OCOCH3)C6H4CH2		24	199	B
148	7-Br	4-OHC6H4CH2		15	283	B
149	7-Br	3,4-(OCH2O)C6H4CH2		57	234	A
150	7-Br	3,5-(CH3O)2C6H4CH2		21	168	A
151	7-Br	3,4,5-(CH3O)3C6H2CH2		21	199-201	A
152	7-Br			4	-	B
153	7-Br	n-butyl		13	130	B
154	7-Br	CH(C6H5)COOCH3		55	187	A
155	7-Br	(E) C6H5CH=CHCH2		10	206	B
156	7-Br	CH(C6H5)COOCH3		32	83	B
157	7-CH3	(E) C6H5CH=CHCH2		43	193	A
158	7-CH3	(E) C6H5CH=CHCH2		35	225	A
159	8-CH3	CH3		70	-	A

N° Compound	X1	R	NR4R5	Yield (%)	MP (°C)	Method
160	8-CH3	(E) C6H5CH=CHCH2		18	-	A
161	7-OH	(E) C6H5CH=CHCH2		10	255	A
162	7- 	(E) C6H5CH=CHCH2		28	-	A

**Compound 109 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.85 (m. 8H) ; 3.3 – 3.45 (m. 4H) ; 5.85 (d. 2H) ; 6.35 – 6.45 (dt. 1H) ; 6.65 – 6.75 (d. 1H) ; 7.25 (t. 1H) ; 7.35 (t. 1H) ; 7.45 (d. 1H) ; 7.6 (t. 1H) ; 7.85 (t. 1H) ; 8.2 (d. 1H) ; 8.3 (d. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 110 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.65 – 1.95 (m. 8H) ; 3.35 (m. 4H) ; 4.8 (d. 2H) ; 5.25 – 5.4 (m. 2H) ; 5.9 – 6.1 (m. 1H) ; 7.55 – 8.4 (m. 3H)

Solvent :  $\text{CDCl}_3$

**- Compound 111 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm): 1.7 – 1.9 (m. 8H) ; 3.35 (m. 4H) ; 5.25 (s. 2H) ; 7.2 – 7.4 (m. 3H) ; 7.45 (d. 2H) ; 7.6 (d. 1H) ; 8.15 (d. 1H) ; 8.4 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 112 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.9 (m. 8H) ; 2.3 (s. 3H) ; 3.35 (m. 4H) ; 5.25 (s. 2H) ; 7.1 – 8.45 (m. 7H)

Solvent :  $\text{CDCl}_3$

**- Compound 113 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.95 (m. 8H) ; 3.4 (m. 4H) ; 5.45 (s. 2H) ; 7.15 – 7.3 (m. 3H) ; 7.4 (d. 1H) ; 7.65 (d. 1H) ; 8.2 (d. 1H) ; 8.45 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 114 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 5.25 (s. 2H) ; 7.2 – 7.4 (m. 3H) ; 7.45 (s.  
5 1H) ; 7.6 (d. 1H) ; 8.15 (d. 1H) ; 8.45 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 115 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.65 – 1.85 (m. 8H) ; 3.3 (m. 4H) ; 5.15 (s. 2H) ; 7.25 (d. 2H) ; 7.35 (d.  
10 2H) ; 7.55 (d. 1H) ; 8.05 (d. 1H) ; 8.3 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 116 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.95 (m. 8H) ; 3.35 (m. 4H) ; 5.25 (d. 2H) ; 7.35 (d. 2H) ; 7.45 (d.  
15 2H) ; 7.6 (d. 1H) ; 8.1 (d. 1H) ; 8.4 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 117 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.9 (m. 8H) ; 3.35 (m. 4H) ; 5.35 (s. 2H) ; 7.5 – 7.7 (m. 5H) ; 8.15  
20 (d. 1H) ; 8.4 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 118 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 5.35 (s. 2H) ; 7.5 – 7.7 (m. 5H) ; 8.1 (d.  
25 1H) ; 8.4 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 119 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 3.9 (s. 3H) ; 5.35 (s. 2H) ; 6.9 (m. 2H) ;  
30 7.2 (d. 1H) ; 7.3 (t. 1H) ; 7.6 (d. 1H) ; 8.2 (d. 1H) ; 8.4 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 120 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 2.0 (m. 8H) ; 3.35 (m. 4H) ; 3.75 (s. 3H) ; 5.4 (s. 2H) ; 6.8 (m. 1H) ;  
7.15 – 7.3 (m. 3H) ; 7.7 (d. 1H) ; 8.35 (m. 2H)  
Solvent :  $\text{CDCl}_3$

5 - **Compound 121** :

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.9 (m. 8H) ; 3.35 (m. 4H) ; 3.8 (s. 3H) ; 5.2 (s. 2H) ; 6.85 (d. 2H) ;  
7.45 (d. 2H) ; 7.65 (d. 1H) ; 8.15 (d. 1H) ; 8.45 (s. 1H)  
Solvent :  $\text{CDCl}_3$

10

- **Compound 122** :

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 5.2 (s. 2H) ; 7.3 (d. 1H) ; 7.4 (d. 1H) ;  
7.5 (s. 1H) ; 7.6 (d. 1H) ; 8.15 (d. 1H) ; 8.4 (s. 1H)  
Solvent :  $\text{CDCl}_3$

15

- **Compound 123** :

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 3.85 (s. 3H) ; 3.90 (s. 3H) ; 5.2 (s. 2H) ;  
6.85 (d. 1H) ; 7.1 (m. 2H) ; 7.65 (d. 1H) ; 8.2 (d. 1H) ; 8.45 (s. 1H)  
Solvent :  $\text{CDCl}_3$

20

- **Compound 124** :

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.65 – 1.95 (m. 8H) ; 3.4 (m. 4H) ; 5.45 (s. 2H) ; 7.2 (m. 1H) ; 7.3 (d.  
1H) ; 7.65 (m. 2H) ; 8.2 (d. 1H) ; 8.4 (s. 1H) ; 8.55 (d. 1H)  
Solvent :  $\text{CDCl}_3$

25

- **Compound 125** :

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.95 (m. 8H) ; 3.4 (m. 4H) ; 5.3 (s. 2H) ; 7.25 (m. 1H) ; 7.6 (d.  
1H) ; 7.85 (d. 1H) ; 8.15 (d. 1H) ; 8.45 (s. 1H) ; 8.6 (d. 1H) ; 8.75 (s. 1H)  
Solvent :  $\text{CDCl}_3$

30

- **Compound 126** :

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.55 – 1.9 (m. 8H) ; 3.1 (t. 2H) ; 3.25 (m. 4H) ; 4.25 (t. 2H) ; 7.05 – 7.25  
(m. 5H) ; 7.55 (d. 1H) ; 8.1 (d. 1H) ; 8.35 (s. 1H)  
Solvent :  $\text{CDCl}_3$

**- Compound 127 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.75 – 1.9 (m. 8H) ; 3.15 (t. 2H) ; 3.35 (m. 4H) ; 3.75 (s. 3H) ; 4.35 (t. 2H) ; 6.8 (d. 2H) ; 7.15 (d. 2H) ; 7.6 (d. 1H) ; 8.15 (d. 1H) ; 8.4 (s. 1H)

5 Solvent :  $\text{CDCl}_3$

**- Compound 128 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.95 (m. 8H) ; 2.2 (m. 2H) ; 2.7 (t. 2H) ; 3.35 (m. 4H) ; 4.2 (t. 2H) ; 7 – 7.3 (m. 5H) ; 7.65 (d. 1H) ; 8.1 (d. 1H) ; 8.45 (s. 1H)

10 Solvent :  $\text{CDCl}_3$

**- Compound 129 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 3.9 (s. 3H) ; 5.6 (s. 2H) ; 7.0 (d. 2H) ; 7.7 (d. 1H) ; 8 (d. 2H) ; 8.25 (d. 1H) ; 8.45 (s. 1H)

15 Solvent :  $\text{CDCl}_3$

**- Compound 130 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.6-1.9(m.8H) ; 3.4(m.4H) ; 5.8(s.2H) ; 7.6(t.2H) ; 7.75(t.1H) ; 7.95(d.1H) ; 8.1(m.3H) ; 8.3(d.1H)

20 Solvent : DMSO

**- Compound 131 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.95 (m. 8H) ; 3.4 (m. 4H) ; 5.55 (s. 2H) ; 7.45 (d. 2H) ; 7.65 (d. 1H) ; 7.9 (d. 2H) ; 8.2 (d. 1H) ; 8.4 (s. 1 H)

25 Solvent :  $\text{CDCl}_3$

**- Compound 132 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 3.9 (s. 3H) ; 4.0 (s. 3H) ; 5.6 (s. 2H) ; 7.1 (d. 1H) ; 7.7 (d. 1H) ; 8.1 (d. 1H) ; 8.2 (d. 1 H) ; 8.4 (m. 2H)

30 Solvent :  $\text{CDCl}_3$

**- Compound 133 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.75 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 3.9 (s. 3H) ; 4.0 (s. 3H) ; 5.6 (s. 2H) ; 7.1 (m. 1H) ; 7.7 (m. 1H) ; 8.15 – 8.45 (m. 4H)



Solvent :  $\text{CDCl}_3$

**- Compound 134:**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.75 – 1.9 (m. 8H) ; 3.35 (m. 4H) ; 5.25 (s. 2H) ; 7.25 - 8.6 (m. 7 H)

5 Solvent :  $\text{CDCl}_3$

**- Compound 135 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.65 – 1.95 (m. 8H) ; 3.3 – 3.45 (m. 4H) ; 5.25 (s. 2H) ; 6.95 – 7.1 (m. 2H) ; 7.4 – 7.55 (m. 2H) ; 7.8 (d. 1H) ; 8.1 (d. 1H) ; 8.6 (s. 1H)

10 Solvent :  $\text{CDCl}_3$

**- Compound 136 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.75 – 1.95 (m. 8H) ; 3.3 – 3.45 (m. 4H) ; 5.3 (s. 2H) ; 7.5 – 7.7 (m. 4H) ; 7.8 (m. 1H) ; 8.1 (dd. 1H) ; 8.6 (s. 1H)

15 Solvent :  $\text{CDCl}_3$

**- Compound 137 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.9 (m. 8H) ; 3.25 – 3.4 (m. 4H) ; 3.8 (s. 3H) ; 3.82 (s. 3H) ; 5.2 (s. 2H) ; 6.8 (d. 1H) ; 7.05 – 7.1 (m. 2H) ; 7.75 (d. 1H) ; 8.05 (d. 1H) ; 8.6 (s. 1H)

20 Solvent :  $\text{CDCl}_3$

**- Compound 138 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.6 – 1.85 (m. 8H) ; 3.2 - 3.4 (bs. 4H) ; 3.55 (s. 2H) ; 5.2 (s. 2H) ; 7.2 (m. 2H) ; 7.3 (m. 2H) ; 8 (m. 1H) ; 8.2 (m. 1H) ; 8.25 (s. 1H) ; 12.3 (bs. 1H)

25 Solvent : DMSO

**- Compound 139 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.75 – 1.9 (m. 8H) ; 3.4 (m. 4H) ; 5.35 (s. 2H) ; 7.3 (m. 1H) ; 7.8 (d. 1H) ; 7.9 (d. 1H) ; 8.1 (d. 1H) ; 8.65 (m. 2H) ; 8.8 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 140 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.8 – 1.95 (m. 8H) ; 3.4 (m. 4H) ; 4.9 (d. 2H) ; 6.35 (m. 1H) ; 6.75 (d. 1H) ; 7.25 – 7.45 (m. 5H) ; 7.8 – 8.65 (m. 3H)

35

Solvent :  $\text{CDCl}_3$

**- Compound 141 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.35 – 2.05 (m. 6H) ; 2.95 (t. 2H) ; 3.4 (d. 2H) ; 4.9 (d. 2H) ; 6.35 (dt.  
5 1H) ; 6.75 (d. 1H) ; 7.25 – 7.45 (m. 5H) ; 7.85 (d. 1H) ; 8.15 (d. 1H) ; 8.65 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 142 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.1 (m. 4H) ; 3.3 - 3.4 (m. 4H) ; 5.25 (s. 2H) ; 7.25 (d. 2H) ; 7.4 (d.  
10 2H) ; 7.75 (d. 1H) ; 7.95 (d. 1H) ; 8.55 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 143 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.95 – 2.1 (m. 4H) ; 3.3 - 3.45 (m. 4H) ; 5.2 (s. 2H) ; 6.95 – 7.1 (m. 2H) ;  
15 7.35 – 7.5 (m. 2H) ; 7.75 (d. 1H) ; 7.95 (d. 1H) ; 8.6 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 144 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.15 (m. 4H) ; 3.3 - 3.45 (m. 4H) ; 5.3 (s. 2H) ; 7.55 – 7.7 (m. 4H) ;  
20 7.8 – 7.9 (d. 1H) ; 8.0 (d. 1H) ; 8.6 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 145 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.1 (m. 4H) ; 3.3 - 3.4 (m. 4H) ; 3.9 (s. 3H) ; 5.3 (s. 2H) ; 7.5 (d.  
25 2H) ; 7.8 (d. 1H) ; 7.9 – 8.05 (m. 3H) ; 8.6 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 146 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.1 (m. 4H) ; 3.3 - 3.4 (m. 4H) ; 3.8 (s. 3H) ; 5.2 (s. 2H) ; 6.9 (d. 2  
30 H) ; 7.45 (d. 2H) ; 7.8 (d. 1H) ; 7.95 (d. 1H) ; 8.6 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 147 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.1 (m. 4H) ; 2.3 (s. 3H) ; 3.3 – 3.4 (m. 4H) ; 5.25 (s. 2H) ; 7.05 (d. 2H) ; 7.5 (d. 2H) ; 7.8 (d. 1H) ; 8.0 (d. 1H) ; 8.6 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 148 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.7 (s. 6H) ; 5 (s. 2H) ; 6.6 (d. 2H) ; 7.1 (d. 2H) ; 7.9 (d. 1H) ; 8.0 (d. 1H) ; 8.1 (s. 1H) ; 9.35 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 149 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.15 (m. 4H) ; 3.3 - 3.45 (m. 4H) ; 5.15 (s. 2H) ; 5.9 (s. 2H) ; 6.75 (d. 1H) ; 6.9 – 7.0 (m. 2H) ; 7.8 (d. 1H) ; 7.9 (d. 1H) ; 8.6 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 150 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.0 – 2.1 (m. 4H) ; 3.3 - 3.4 (m. 4H) ; 3.75 (s. 6H) ; 5.2 (s. 2H) ; 6.4 (s. 1H) ; 6.65 (s. 2H) ; 7.8 (d. 1H) ; 7.95 (d. 1H) ; 8.65 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 151 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.0 – 2.1 (m. 4H) ; 3.3 - 3.4 (m. 4H) ; 3.85 (s. 3H) ; 3.9 (s. 6H) ; 5.2 (s. 2H) ; 6.8 (s. 2H) ; 7.8 (d. 1H) ; 7.95 (d. 1H) ; 8.65 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 152 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 (m. 4H) ; 3.35 (m. 4H) ; 5.2 (s. 2H) ; 7.15 (s. 1H) ; 7.6 (s. 1H) ; 8 – 8.15 (m. 2H) ; 8.3 (s. 1H) ; 12 (m. 1H)

Solvent : DMSO

**- Compound 153 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 0.95 (t. 3H) ; 1.35 – 1.5 (m. 2H) ; 1.8 – 1.9 (m. 2H) ; 2.0 – 2.1 (m. 4H) ; 3.4 - 3.5 (m. 4H) ; 4.1 (t. 2H) ; 7.8 (d. 1H) ; 8.0 (d. 1H) ; 8.6 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 154 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.45 – 2.55 (m. 4H) ; 3.25 - 3.4 (m. 4H) ; 3.7 (s. 3H) ; 6.6 (s. 1H) ; 7.35 – 7.50 (m. 3H) ; 7.55 (d. 2H) ; 8 – 8.1 (m. 2H) ; 8.3 (s. 1H)

5 Solvent : DMSO

**- Compound 155 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.9 (s. 6H) ; 4.8 (d. 2H) ; 6.2 – 6.3 (dt. 1H) ; 6.7 (d. 1H) ; 7.1 – 7.35 (m. 5H) ; 7.75 (d. 1H) ; 8.0 (d. 1H) ; 8.6 (s. 1H)

10 Solvent :  $\text{CDCl}_3$

**- Compound 156 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.9 (s. 6H) ; 3.8 (s. 3H) ; 6.6 (s. 1H) ; 7.35 – 7.45 (m. 3H) ; 7.55 (d. 2H) ; 7.8 (d. 1H) ; 8 (d. 1H) ; 8.6 (s. 1H)

15 Solvent :  $\text{CDCl}_3$

**- Compound 157 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.8 – 1.95 (m. 8H) ; 2.5 (s. 3H) ; 3.4 – 3.5 (m. 4H) ; 4.9 (d. 2H) ; 6.3 – 6.45 (dt. 1H) ; 6.7 – 6.8 (d. 1H) ; 7.2 – 7.3 (m. 3H) ; 7.35 (d. 2H) ; 7.55 (d. 2H) ; 8.1 (d. 1H) ; 8.3 (s. 1H)

20 Solvent :  $\text{CDCl}_3$

**- Compound 158 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.1 (m. 4H) ; 2.5 (s. 3H) ; 3.4 (m. 4H) ; 4.9 (d. 2H) ; 6.3 – 6.45 (dt. 1H) ; 6.7 – 6.8 (d. 1H) ; 7.2 – 7.4 (m. 5H) ; 7.5 (m. 1H) ; 8 (d. 1H) ; 8.3 (d. 1H)

25 Solvent :  $\text{CDCl}_3$

**- Compound 159 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.9 (m. 8H) ; 2.45 (s. 3H) ; 3.25 – 3.35 (m. 4H) ; 3.65 (s. 3H) ; 7.2 – 7.3 (m. 2H) ; 8 (m. 1H) ; 8.2 - 8.3 (m. 1H)

30 Solvent :  $\text{CDCl}_3$

**- Compound 160 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.8 – 2 (m. 8H) ; 2.55 (s. 3H) ; 3.3 - 3.5 (m. 4H) ; 4.9 (m. 2H) ; 6.3 – 6.4 (m. 1H) ; 6.7 – 6.8 (d. 1H) ; 7.2 – 7.4 (m. 6H) ; 8.1 (s. 1H) ; 8.35 (m. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 161 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 (m. 4H) ; 3.4 (m. 4H) ; 4.8 (d. 2H) ; 6.35 – 6.4 (dt. 1H) ; 6.7 (d. 1H) ; 7.2 – 7.4 (m. 4H) ; 7.45 (d. 2H) ; 7.55 (s. 1H) ; 8 (d. 1H) ; 10 (m. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 162 :**

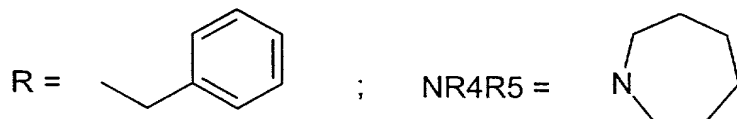
N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.5 – 2.1 (m. 16H) ; 3.3 - 3.7 (m. 8H) ; 4.9 (d. 2H) ; 6.3 – 6.4 (dt. 1H) ; 6.7 – 6.8 (d. 1H) ; 6.8 – 6.9 (d. 1H) ; 7.2 – 7.5 (m. 6H) ; 8.25 (d. 1H)

Solvent :  $\text{CDCl}_3$

**Example 163**

**METHOD A :** 1-Azepanyl-4-benzyl-7-bromo-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

(I) :  $\text{X1} = 7\text{-Br}$  ;  $\text{X2} = \text{H}$  ;



In a 50 ml balloon flask protected from humidity, we resuspend 4.0 g (10,7 mmol) of 4-benzyl-1,7-dibromo-4H-[1,2,4] triazolo [4,3-a]quinazolin-5-one (prepared by method of example 256) 25 ml of hexamethylene imine.

The mixture is then heated by reflux, under shaking, for 16 hours.

After cooling down, the obtained solution is concentrated under vacuum to give 4.8 g of residue which is purified by flash chromatography on silica column, by elution with the mixture  $\text{CH}_2\text{Cl}_2$  99.6 /  $\text{CH}_3\text{OH}$  0.4.

The fractions pure in CCM are joined, evaporated until dry and the obtained product (4.0 g) is recrystallized in ethanol.

We obtain 3.2 g of compound from example 163 as crystals.

Yield = 66 %.

F (Tottoli) =  $175^\circ\text{C}$

CCM (CH<sub>2</sub> Cl<sub>2</sub> 99 / CH<sub>3</sub> OH 1) : R<sub>f</sub> = 0.40

NMR <sup>1</sup>H δ (ppm) CDCl<sub>3</sub> :

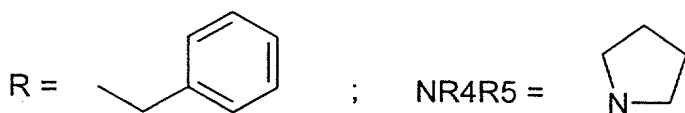
1.7 – 1.85 (m. 8H) ; 3.3 (m. 4H) ; 5.3 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.45 –d. 2H) ; 8.0 (d. 1H) ; 8.15 (s. 1H) ; 8.4 (d. 1H)

5

#### Example 164

**METHOD B** : 1-(Pyrrolidin-1-yl)-4-benzyl-7-bromo-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

(I) : X<sub>1</sub> = 7-Br ; X<sub>2</sub> = H ;



10

In a reactor protected from humidity, we resuspend 37.0 g (85 mmol) of 4-benzyl-1,7-dibromo-4H-[1,2,4] triazolo [4,3-a]quinazolin-5-one in 750 ml of dimethylformamide (DMF) and add 14.3 g (340 mmol) of sodium bicarbonate then 12.1 g (340 mmol) of pyrrolidine.

15

The mixture is then heated by reflux, under shaking, for 6 hours.

After cooling down, the solvent is evaporated under vacuum, the obtained residue is resuspended in a mixture water / ethyl acetate and the insoluble fraction is triturated then filtered and dried : we obtain then from a first round 18.3g of compound from example 164, this compound being pure by CCM.

20

The aqueous and organic phases are separated, the ethyl acetate phase is washed in water and dried on Na<sub>2</sub>SO<sub>4</sub>. After solvent concentration under vacuum, we obtain from a second round 14.2g of compound from example 164, also pure by CCM.

Yield (as crude product) = 90% ; the product will be used like this in the next step.

A 0.35g sample is recrystallized in methanol to give 0.32g of pure compound as crystal.

25

F (Tottoli) = 173°C

CCM (CH<sub>2</sub>Cl<sub>2</sub> 99 / CH<sub>3</sub>OH 1) = 0.35

N.M.R. <sup>1</sup>H δ (ppm) : 2.1 (m. 4H) ; 3.4 (m. 4H) ; 5.45 (s. 2H) ; 7.3 (m. 3H) ; 7.65 (d. 2H) ; 7.85 (d. 1H) ; 8.15 (d. 1H) ; 8.45 (s. 1H)

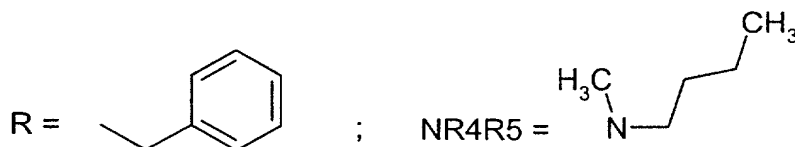
Solvent : CDCl<sub>3</sub>

30

### Example 165

**METHOD C** : 1-[N-(n-butyl), N-methylamino]-4-benzyl-7-bromo-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

(I) : X1 = 7-Br ; X2 = H



In a pressure reactor, we resuspend 2.5 g (5,75 mmol) of 4-benzyl-1,7-dibromo-4H-[1,2,4] triazolo [4,3-a]quinazolin-5-one in 30 ml of ethanol. We add 5.0g of n-butyl-methylamine (57.5 mmol), we hermetically seal the reactor then we heat in an oil bath at 160°C for 8 hours.

10      After cooling down and leaving aside for 2 days, the residual oil (2.8g) is chromatographed on silica column by elution with the mixture CH<sub>2</sub>Cl<sub>2</sub> 99.5 – CH<sub>3</sub>OH 0.5. We obtain 1.8 g of compound from example 165.

Yield = 70 %.


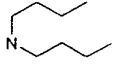

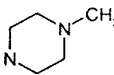
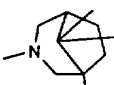











CCM (CH<sub>2</sub> Cl<sub>2</sub> 98.5 / CH<sub>3</sub> OH 1.5) : R<sub>f</sub> = 0.45

15      N.M.R. <sup>1</sup>H δ (ppm) : 0.9 (t. 3H) ; 1.25 – 1.4 (m. 2H) ; 1.55 – 1.7 (m. 2H) ; 2.85 (s. 3H) ; 2.9 – 3.5 (m. 2H) ; 5.5 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.25 (d. 1H) ; 8.5 (s. 1H)

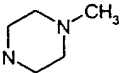
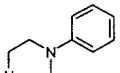
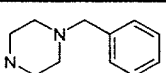


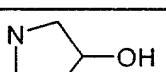










Solvent : CDCl<sub>3</sub>

20      The compounds (I) from examples 166 to 198 (table 3) are prepared according to one of the methods A, B or C described in examples 163 to 165.

TABLE3

N° Compound	X1	R	NR4R5	Yld (%)	MP (°C)	Method
166	H	C6H5CH2		70	167	B
167	7-Cl	CH3		17	112	A
168	7-Cl	CH3		35	192	A
169	7-Cl	CH3		50	180-182	A
170	7-Cl	CH3		60	185	A
171	7-Cl	C6H5		5	179	A
172	7-Cl	C6H5CH2		88	162	A
173	7-Cl	C6H5CH2		78	163	B
174	7-Cl	C6H5CH2		68	178	B
175	8-Cl	CH3		11	179	A
176	8-Cl	C6H5CH2		1	-	B
177	7-Br	CH3		72	174	A
178	7-Br	C6H5CH2		67	183-185	A
179	7-Br	C6H5CH2		53	171	B
180	7-Br	C6H5CH2		50	189	B
181	7-Br	C6H5CH2		49	235	B



N° Compound	X1	R	NR <sub>4</sub> R <sub>5</sub>	Yld (%)	MP (°C)	Method
182	7-Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		60	230	B
183	7-Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		51	238	B
184	7-Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		50	226	B
185	7-Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		82	172	B
186	7-Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		85	210	B
187	7-Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		79	176	B
188	7-Br	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	NHCH <sub>3</sub>	52	238	C
189	7-I	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		100	184	B
190	7-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		90	183	B
191	7-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		60	189	B
192	7-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		75	186	B
193	7-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		78	265	B
194	8-CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		50	202	A
195	7-OCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		42	153	B
196	7-OCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		65	154	B
197	7-CN	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		77	219	B
198	7-NO <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		32	206	A

**- Compound 166 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 (m. 4H) ; 3.3 (m. 4H) ; 5.35 (s. 2H) ; 7.2 – 7.3 (m. 3H) ; 7.4 (d. 2H) ; 7.6 (t. 1H) ; 7.9 (t. 1H) ; 8.2 (m. 2H)

Solvent : DMSO

**- Compound 167 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 0.8 (m. 6H) ; 1.15 – 1.25 (m. 4H) ; 1.35 – 1.55 (m. 4H) ; 3 (m. 2H) ; 3.2 (m. 2H) ; 3.7 (s. 3H) ; 7.65 (m. 1H) ; 8.3 (m. 1H) ; 8.45 (m. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 168 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.3-1.9 (m. 6H) ; 2.9 (t. 2H) ; 3.3 (m. 2H) ; 3.5 (s. 3H) ; 8.0 (d. 1H) ; 8.1 (d. 1H) ; 8.3 (d. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 170 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 0.7 (s. 3H) ; 0.8 (s. 3H) ; 1.0 (s. 3H) ; 1.5-1.9 (m. 5H) ; 2.55 (d. 1H) ; 2.85 (d. 1H) ; 3.15 (m. 4H) ; 3.4 (m. 4H) ; 7.9 (d. 1H) ; 8.0 (s. 1H) ; 8.4 (m. 1H)

Solvent : DMSO

**- Compound 171 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.8 (m. 8H) ; 3.3 (m. 4H(+ $\text{H}_2\text{O}$ )) ; 7.45 – 7.6 (m. 5H) ; 8.05 (m. 1H) ; 8.15 (s. 1H) ; 8.45 (d. 1H)

Solvent : DMSO

**- Compound 172 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.85 (m. 8H) ; 3.3 (s. 4H) ; 5.3 (s. 2H) ; 7.25 – 7.5 (m. 5H) ; 8.0 (m. 1H) ; 8.15 (d. 1H) ; 8.4 (d. 1H)

Solvent : DMSO

**- Compound 173 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.05 (m. 4H) ; 3.4 (m. 4H) ; 5.45 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.65 – 7.75 (m. 3H) ; 8.2 (dd. 1H) ; 8.35 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 174 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.4 – 1.6 (m. 1H) ; 1.7 - 2 (m. 4H) ; 3 - 3.15 (m. 2H) ; 3.3 – 3.45 (m. 2H) ; 5.45 (s. 2H) ; 7.25 – 7.35 (m. 3H) ; 7.7 – 7.8 (m. 3H) ; 8.3 – 8.4 (m. 2H)

Solvent :  $\text{CDCl}_3$

**- Compound 175 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.85 – 1.95 (m. 4H) ; 3.4 (m. 4H +  $\text{H}_2\text{O}$ ) ; 3.65 (s. 3H) ; 7.7 (d. 1H) ; 8.3 (d. 1H) ; 8.55 (s. 1H)

Solvent : DMSO

**- Compound 176 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.8 – 2 (m. 8H) ; 3.3 – 3.5 (m. 4H) ; 5.4 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.4 – 7.45 (m. 2H) ; 7.65 – 7.7 (m. 2H) ; 8.25 – 8.3 (m. 2H) ; 8.6 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 177 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.85 (m. 8H) ; 3.4 (m. 4H) ; 3.7 (s. 3H) ; 7.75 (m. 1H) ; 8.25 (m. 1H) ; 8.4 (m. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 178 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.35 – 1.95 (m. 6H) ; 3.05 (t. 2H) ; 3.35 (d. 2H) ; 5.45 (s. 2H) ; 7.3 (m. 3H) ; 7.75 (d. 2H) ; 7.95 (d. 1H) ; 8.3 (d. 1H) ; 8.5 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 179 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.9 (s. 6H) ; 5.5 (s. 2H) ; 7.25 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.85 (d. 1H) ; 8.2 (d. 1H) ; 8.5 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 180 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 3.2 – 3.4 (m. 4H) ; 3.75 – 3.9 (m. 2H) ; 3.9 – 4.1 (m. 2H) ; 5.5 (s. 2H) ; 7.2 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.25 (d. 1H) ; 8.5 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 181 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.8 – 3.0 (m. 4H) ; 3.35 – 3.5 (m. 2H) ; 3.5 – 3.7 (m. 2H) ; 5.45 (s. 2H) ;  
5 7.2 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.2 (d. 1H) ; 8.5 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 182 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.3 – 2.45 (m. 5H) ; 2.9 – 3.0 (m. 2H) ; 3.25 – 3.35 (m. 4H) ; 5.5 (s. 2H) ;  
10 7.2 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.25 (d. 1H) ; 8.5 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 183 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 3.0 – 3.2 (m. 2H) ; 3.35 – 3.5 (m. 4H) ; 3.6 – 3.75 (m. 2H) ; 5.5 (s. 2H) ;  
15 6.9 – 7.05 (m. 3H) ; 7.2 – 7.35 (m. 5H) ; 7.7 (d. 2H) ; 7.85 (d. 1H) ; 8.3 (d. 1H) ; 8.55 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 184 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.4 (m. 2H) ; 3 (m. 2H) ; 3.3 (m. 4H) ; 5.5 (s. 2H) ; 7.3 (m. 8H) ; 7.7 (m.  
20 2H) ; 7.9 (d. 1H) ; 8.2 (d. 1H) ; 8.5 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 185 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.2 – 2.65 (m. 2H) ; 3.2 – 3.9 (m. 4H) ; 5.45 (s. 2H) ; 5.8 – 5.9 (m. 1H) ;  
25 5.9 – 6.0 (m. 1H) ; 7.2 – 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.25 (d. 1H) ; 8.5 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 186 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 4.3 (s. 4H) ; 5.5 (s. 2H) ; 5.95 (s. 2H) ; 7.25 – 7.4 (m. 3H) ; 7.7 (d. 2H) ;  
30 7.9 (d. 1H) ; 8.25 (d. 1H) ; 8.5 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 187 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 - 2.1 (m. 1H) ; 2.3 - 2.4 (m. 1H) ; 3.2 - 3.6 (m. 5H) ; 4.6 - 4.7 (m. 1H) ; 5.45 (s. 2H) ; 7.2 - 7.3 (m. 3H) ; 7.65 (d. 1H) ; 7.85 (d. 1H) ; 8.3 (d. 2H) ; 8.5 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 188 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 3.05 (s. 3H) ; 3.9 - 4.0 (m. 1H) ; 5.35 (s. 2H) ; 7.15 - 7.25 (m. 3H) ; 7.6 (d. 2H) ; 7.7 (d. 1H) ; 7.95 (d. 1H) ; 8.4 (s. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 189 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 (m. 4H) ; 3.4 (m. 4H) ; 5.3 (s. 2H) ; 7.3 (m. 3H) ; 7.4 (m. 2H) ; 8.0 (m. 1H) ; 8.2 (m. 1H) ; 8.5 (m. 1H)

Solvent : DMSO

**- Compound 190 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.75 - 1.95 (m. 8H) ; 2.45 (s. 3H) ; 3.35 - 3.45 (m. 4H) ; 5.45 (s. 2H) ; 7.2 - 7.35 (m. 3H) ; 7.45 (dd. 1H) ; 7.7 (dd. 2H) ; 8.15 (s. 1H) ; 8.3 (d. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 191 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 (m. 4H) ; 2.5 (s. 3H) ; 3.3 (m. 4H) ; 5.3 (s. 2H) ; 7.2 - 7.55 (m. 5H) ; 7.7 (d. 1H) ; 8 (s. 1H) ; 8.15 (d. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 192 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.45 (s. 3H) ; 2.9 (s. 6H) ; 5.45 (s. 2H) ; 7.2 - 7.3 (m. 3H) ; 7.45 (d. 1H) ; 7.7 (d. 2H) ; 8.2 (d. 2H)

Solvent :  $\text{CDCl}_3$

**- Compound 193 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.5 (s. 3H) ; 2.8 - 3.05 (m. 4H) ; 3.35 - 3.75 (m. 4H) ; 5.5 (s. 2H) ; 7.15 - 7.4 (m. 3H) ; 7.6 (d. 1H) ; 7.7 (d. 2H) ; 8.1 - 8.25 (m. 2H)

Solvent :  $\text{CDCl}_3$

**- Compound 194 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.8 – 1.95 (m. 8H) ; 2.55 (s. 3H) ; 3.4 (m. 4H) ; 5.4 (s. 2H) ; 7.25 – 7.35 (m. 4H) ; 7.7 (m. 2H) ; 8.25 (m. 2H)

Solvent :  $\text{CDCl}_3$

**- Compound 195 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.8 – 1.95 (m. 8H) ; 3.35 – 3.40 (m. 4H) ; 3.9 (s. 3H) ; 5.4 (s. 2H) ; 7.25 – 7.35 (m. 4H) ; 7.7 (dd. 2H) ; 7.8 (d. 1H) ; 8.35 (d. 1H)

Solvent :  $\text{CDCl}_3$

**- Compound 196 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 (m. 4H) ; 3.35 (m. 4H) ; 3.9 (s. 3H) ; 5.35 (s. 2H) ; 7.25 – 7.35 (m. 3H) ; 7.45 (d. 2H) ; 7.55 (d. 1H) ; 7.7 (s. 1H) ; 8.2 (d. 1H)

Solvent : DMSO

**- Compound 197 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.4 (m. 4H) ; 3.2 (m. 4H) ; 5.2 (s. 2H) ; 7.1 – 7.25 (m. 3H) ; 7.35 (m. 2H) ; 8.25 (m. 2H) ; 8.5 (s. 1H)

Solvent :  $\text{CDCl}_3$

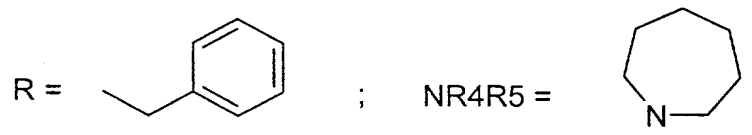
**- Compound 198 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.7 – 1.85 (m. 8H) ; 3.3 (s. 4H +  $\text{H}_2\text{O}$ ) ; 5.35 (s. 2H) ; 7.3 (m. 3H) ; 7.5 (m. 2H) ; 8.55 (d. 1H) ; 8.75 (d. 1H) ; 8.9 (s. 1H)

Solvent : DMSO

**Example 199 :** 1-Azepanyl-4-benzyl-7-chloro-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

(I) \_\_\_\_\_ ;  $\text{X1} = 7\text{-Cl}$  ;  $\text{X2} = \text{H}$



In a 50 ml balloon flask, equipped with a shaker and refrigeration, we resuspend 0.44 g (1,27 mmol) of 4-benzyl-1,7-dichloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (example 254) in 2.5 ml of hexamethylene imine. Under shaking, the mixture is heated by reflux for 16 hours.

- 5 The obtained brown solution is then left aside to ambient temperature until complete cooling down; then we pour in a mixture of water and methylene chloride, shake and separate the 2 phases by decantation. The organic phase is washed twice in water, dried on Na<sub>2</sub>SO<sub>4</sub> then evaporated under vacuum to give 0.59 g of brown solid residue.

This is chromatographed on silica column by elution with the mixture CH<sub>2</sub> Cl<sub>2</sub> 99.5 / CH<sub>3</sub> OH 0.5.

We obtain after joining and evaporation of pure by CCM fractions, 0.46 g of compound from example 199. This is recrystallized in ethanol to give 0.4 g of colorless crystal.

Yield = 77 %

F (Tottoli) = 162°C

- 15 CCM (CH<sub>2</sub> Cl<sub>2</sub> 98.5 / CH<sub>3</sub> OH 1.5) : R<sub>f</sub> = 0.35

N.M.R. <sup>1</sup>H δ (ppm) : 1.7 – 1.85 (m. 8H) ; 3.3 (s. 4H) ; 5.3 (s. 2H) ; 7.25 – 7.5 (m. 5H) ; 8.0 (m. 1H) ; 8.15 (d. 1H) ; 8.4 (d. 1H)

Solvent : DMSO

- 20 The compounds (I) from examples 200 to 214 (table 4) are prepared according to the process from example 199.

TABLE4

N° Compound	X1	R	NR4R5	Yld (%)	MP (°C)	Method
200	H	CH3		40	199 – 203	A
201	H	C6H5CH2		66	157	A
202	6-Cl	CH3		8,5	> 275	A
203	7-Cl	CH3		77	145	A
204	7-Cl	CH3CH2		11	98-100	A
205	7-Cl	CH3		50	203-205	A
206	7-Cl	CH3		25	232	A
207	7-Cl	CH3		25	123-125	A
208	7-Cl	CH3		15	204	A
209	7-Cl	CH3		30	272	A
210	7-Cl	CH3		25	180	A
211	7-Cl	CH3		25	165	A
212	7-F	CH3		13	136	A
213	7-I	CH3		47	206	A
214	7-OCH3	CH3		34	203	A



**- Compound 200 :**

N.M.R.1H  $\delta$  (ppm) : 1.75-1.9 (m. 8H) ; 3.4 (m. 4H) ; 3.6 (s. 3H) ; 7.6 (t. 1H) ; 8 (t. 1H) ; 8.25 (d. 1H) ; 8.4 (d. 1H)

Solvent : DMSO

**- Compound 201 :**

N.M.R.1H  $\delta$  (ppm) : 1.7 - 1.85 (m. 8H) ; 3.3 (m. 4H) ; 5.3 (s. 2H) ; 7.2 - 7.35 (m. 3H) ; 7.45 (d. 2H) ; 7.6 (t. 1H) ; 7.95 (t. 1H) ; 8.2 (d. 1H) ; 8.4 (d. 1H)

Solvent : DMSO

**- Compound 202 :**

N.M.R.1H  $\delta$  (ppm) : 1.5 - 1.8 (m. 8H) ; 3.4 (m. 4H) ; 3.5 (s.3H) ; 7.05 (d. 1H) ; 7.5 (t. 1H) ; 8.4 (d. 1H)

Solvent : DMSO

**- Compound 203 :**

N.M.R.1H  $\delta$  (ppm) : 1.7 - 1.85 (m. 8H) ; 3.3 (m. 4H) ; 3.5 (s. 3H) ; 7.95 (d. 1H) ; 8.1 (s. 1H) ; 8.35 (d. 1H)

Solvent : DMSO

**- Compound 204 :**

N.M.R.1H  $\delta$  (ppm) : 1.3 (t. 3H) ; 1.7 - 1.9 (m. 8H) ; 3.3 (m. 4H) ; 4.15 (q. 2H) ; 7.95 (d. 1H) ; 8.1 (s. 1H) ; 8.35 (d. 1H)

Solvent : DMSO

**- Compound 205 :**

N.M.R.1H  $\delta$  (ppm) : 2.0 (m. 4H) ; 3.35 (m. 4H) ; 3.75 (s. 3H) ; 7.65 (d. 1H) ; 8.15 (d. 1H) ; 8.3 (s. 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 206 :**

N.M.R.1H  $\delta$  (ppm) : 3.1 - 3.35 (m. 4H) ; 3.65 (s. 3H) ; 3.85 (m. 2H) ; 4.0 (m. 2H) ; 7.75 (d. 1H) ; 8.35 (m. 2H)

Solvent : CDCl<sub>3</sub>

**- Compound 207 :**

N.M.R.<sup>1</sup>H δ (ppm) : 1.8 (m. 10H) ; 3.4 (m. 4H) ; 3.75 (s. 3H) ; 7.75 (d. 1H) ; 8.35 (s. 1H) ;  
8.4 (d. 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 208 :**

N.M.R.<sup>1</sup>H δ (ppm) : 2.1 (m. 2H) ; 2.8 - 3.1 (m. 2H) ; 3.65 (m. 1H) ; 3.75 (s. 3H) ; 3.9 (m. 1H) ;  
6.15 (d. 1H) ; 6.75 (t. 1H) ; 6.85 (t. 1H) ; 7.1 (d. 1H) ; 7.5 (d. 1H) ; 7.85 (d. 1H) ; 8.3 (s. 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 209 :**

N.M.R.<sup>1</sup>H δ (ppm) : 2.9 (m. 1H) ; 3.2 (m. 1H) ; 3.4 (m. 1H) ; 3.6 (m. 1H) ; 3.7 (s. 3H) ; 4.3  
(d. 1H) ; 4.45 (d. 1H) ; 7.05 (d. 1H) ; 7.2 (m. 3H) ; 7.6 (d. 1H) ; 8.2 (d. 1H) ; 8.3 (s. 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 210 :**

N.M.R.<sup>1</sup>H δ (ppm) : 1.4 (m. 2H) ; 1.7 (m. 3H) ; 2.6 (d. 2H) ; 2.9 - 3.15 (m. 2H) ; 3.3-3.5 (m.  
2H) ; 3.65 (s. 3H) ; 7.0-7.35 (m. 5H) ; 7.7 (d. 1H) ; 8.3 (m. 2H)

Solvent : CDCl<sub>3</sub>

**- Compound 211 :**

N.M.R.<sup>1</sup>H δ (ppm) : 1 (s. 3H) ; 1.1 (s. 3H) ; 1.25-1.4 (m. 5H) ; 1.45 (d. 1H) ; 1.6 (m. 2H) ; 1.9  
(d. 1H) ; 2.05 (m. 1H) ; 3.35 (d. 1H) ; 3.45 (d. 1H) ; 3.7 (s. 3H) ; 4 (m. 1H) ; 7.65 (d. 1H) ; 8.3  
(s. 1H) ; 8.6 (d. 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 212 :**

N.M.R.<sup>1</sup>H δ (ppm) : 1.7 – 1.8 (m. 8H) ; 3.3 (m. 4H (+H<sub>2</sub>O)) ; 3.5 (s. 3H) ; 7.8 (m. 1H) ; 7.9  
(m. 1H) ; 8.4 (m. 1H)

Solvent : DMSO

**- Compound 213 :**

N.M.R.<sup>1</sup>H δ (ppm) : 1.7 - 1.9 (m. 8H) ; 3.3 (m. 4H) ; 3.7 (s. 3H) ; 8.0 (d. 1H) ; 8.1 (d. 1H) ;  
8.65 (s. 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 214 :**

N.M.R.<sup>1</sup>H δ (ppm) : 1.7 - 1.85 (m. 8H) ; 3.3 (s. 4H) ; 3.5 (s. 3H) ; 3.9 (s. 3H) ; 7.5 (d. 1H) ; 7.6 (s. 1H) ; 8.3 (d. 1H)

Solvent : CDCl<sub>3</sub>

**Example 215 :** 4-benzyl-7-bromo-1-(N-ethyl, N-methylamino)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.3g (0.8 mmol) of 4-benzyl-7-bromo-1-(N-methylamino)-4H-[1,2,4] triazolo-[4,3-a]quinazolin-5-one (compound from example 188) is dissolved in 5ml of DMF. We add 0.135g (0.85 mmol) of methyl iodide and 0.13g (0.93 mmol) of potassium carbonate. The obtained mixture is shaken at ambient temperature for a night then heated at 100°C for 6 hours. After cooling down, the solvent is evaporated under vacuum, the residue is resuspended in water and ethyl acetate. The organic phase is separated by decantation, washed with a saturated solution of sodium chloride, dried on Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum. We obtain 0.3g of crude product which is purified by chromatography on silica column by elution with the mixture CH<sub>2</sub>Cl<sub>2</sub> 99 / CH<sub>3</sub>OH 1. The fractions containing the desired product are joined, concentrated under vacuum then the residue is recrystallized in methanol to give 0.05g of pure compound from example 215.

Yield = 22%

F (Tottoli) = 148°C

CCM (CH<sub>2</sub> Cl<sub>2</sub> 98.5 / CH<sub>3</sub> OH 1.5) : R<sub>f</sub> = 0.45

N.M.R.<sup>1</sup>H δ (ppm) : 1.25 (t. 3H) ; 2.9 (s. 3H) ; 3.2 - 3.4 (m. 2H) ; 5.45 (s. 2H) ; 7.2 - 7.35 (m. 3H) ; 7.7 (d. 2H) ; 7.9 (d. 1H) ; 8.3 (d. 1H) ; 8.5 (s. 1H)

Solvent : CDCl<sub>3</sub>

**Example 216 :** 4-benzyl-1-(N,N-diethyl)- 7-methyl-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

2.3g (5.87 mmol) of 4-benzyl-7-methyl-1-(thiamorpholin-4-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (compound from example 193) are resuspended in 250ml of ethanol. We add a catalytic amount of Raney 's nickel and we heat by reflux, under shaking, for 24 hours. The catalyzer is eliminated by filtration on Celite and the alcoholic solution is concentrated under vacuum : we obtain 1.6g of crude product which is purified by chromatography on

silica column by elution using CH<sub>2</sub>Cl<sub>2</sub> and methanol gradient from 99.5/0.5 to give 0.9g of pure by CCM product. A sample is recrystallized in ethanol to determinate physical parameters.

Yield = 42%

5 F (Tottoli) = 154°C

CCM (CH<sub>2</sub> Cl<sub>2</sub> 99 / CH<sub>3</sub> OH 1) : Rf = 0.35

N.M.R.1H δ (ppm) : 1 - 1.3 (m. 6H) ; 2.4 (s. 3H) ; 2.9 - 3.45 (m. 4H) ; 5.4 (s. 2H) ; 7.1 - 7.3 (m. 3H) ; 7.45 (d. 1H) ; 7.6 (d. 2H) ; 8.15 (s. 1H) ; 8.3 (d. 1H)

Solvent : CDCl<sub>3</sub>

10

**Example 217** : 4-benzyl-7-bromo-1-(pyrrol-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a 25ml balloon flask, we resuspend 0.7g (1.8 mmol) of 1-amino-4-benzyl-7-bromo-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (intermediate 10 compound of example 271) in 5ml of acetic acid. We add 0.25g (1.9 mmol) of 2,5-dimethoxytetrahydrofuran then heat the mixture by reflux for 1 hour. After cooling down and evaporation of acetic acid under vacuum, we obtain 0.8g of highly colored solid which is purified by chromatography on silica column by elution with the mixture CH<sub>2</sub>Cl<sub>2</sub> / CH<sub>3</sub>OH (99,4/0,6 then 99/1). The solid obtained from pure fractions is recrystallized in ethanol to give 0,45g of compound from example 217.

20

Yield = 55%

F (Tottoli) = 214°C

CCM (CH<sub>2</sub> Cl<sub>2</sub> 99 / CH<sub>3</sub> OH 1) : Rf = 0.5

N.M.R.1H δ (ppm) : 5.55 (s. 2H) ; 5.8 (d. 1H) ; 6.5 (s. 2H) ; 6.9 (s. 2H) ; 7.25 - 7.4 (m. 3H) ; 7.7 (d. 1H) ; 7.75 (d. 2H) ; 8.55 (s. 1H)

25

Solvent : CDCl<sub>3</sub>

**Example 218** : 4-(4-aminobenzyl)-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

30

In a 50ml balloon flask, we resuspend 0.45g (0.96 mmol) of 7-bromo-4-(4-nitrobenzyl)-1-(pyrrol-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (compound from example 48) in 10ml ethanol. We add 1.08g (24 mmol) of dehydrate stannous chloride then heat at 70°C, under shaking, for 30 minutes. After cooling down, the mixture is poured into iced water. We

extract several times by ethyl acetate with a little of  $\text{CHCl}_3$ , the organic phase is washed in a solution sodium chloride saturated, dried on  $\text{Na}_2\text{SO}_4$  then concentrated under vacuum. The obtained solid residue (0.35g) is washed in methanol (50ml) to give 0.25g of pure by CCM product.

5 Yield = 83%

F (Tottoli) =  $263^\circ\text{C}$

CCM ( $\text{CH}_2\text{Cl}_2$  98 /  $\text{CH}_3\text{OH}$  2) :  $R_f = 0.25$

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 1.9 - 2.05 (m. 4H) ; 3.3 - 3.4 (m. 4H) ; 5 (s. 2H) ; 5.1 (s. 2H) ; 6.5 (d. 2H) ; 7.2 (d. 2H) ; 8.1 (d. 1H) ; 8.2 (d. 1H) ; 8.3 (s. 1H)

10 Solvent : DMSO

**Example 219 :** 4-(benzyl)-7-hydroxy-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

15 **Example 219-1/** 4-benzyl-7-(4-tolylsulfonyloxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a reactor equipped with a shaker and refrigeration, we resuspend 1.46g (5 mmol) of 4-benzyl-7-hydroxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (intermediate obtained by method from example 255) in 15ml of dry methylene chloride. We add 0.95g (5 mmol) of tosyl chloride and then add, under shaking within 5 minutes, 1ml (7.5 mmol) of triethylamine, the reaction being slightly exothermic. After additional shaking at ambient temperature for 2 hours, the obtained organic solution is washed in water and dried on  $\text{Na}_2\text{SO}_4$  to give, after solvent evaporation, a colored amorphous residue which is purified by chromatography on silica column by elution with ethyl acetate. We obtain 1.9g of pure product by CCM. This one  
20 will be used like this in the next step.

25 Yield = 85%

2/ **Example 219-2/** 4-benzyl-1-bromo-7-(4-tolylsulfonyloxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

30 0.4g of this compound is obtained from 0.45g of 4-benzyl-7-(4-tolylsulfonyloxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (example 219-1) by bromination method described in example 256.

Yield = 76%

3/ Example 219-3/ 4-benzyl-1-(pyrrolidin-1-yl)-7-(4-tolylsulfonyloxy)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one and 4-benzyl-7-hydroxy-1-(pyrrolidin-1-yl)- 4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.83g of the brominated derived obtained in example 219-2 is treated by pyrrolidine in conditions of example 164. After treatment, we obtain 1.0g of crude mixture of 2 majoritary compounds which are separated by chromatography on silica column after elution with the mixture CH<sub>2</sub>Cl<sub>2</sub> 98 / CH<sub>3</sub>OH 2. The fractions containing the first pure product are joined and concentrated to give 0.375g of 4-benzyl-1-(pyrrolidin-1-yl)-7-(4-tolylsulfonyloxy)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

Yield = 45%

The fractions containing the second pure product are joined and evaporated under vacuum to give 0.12g of 4-benzyl-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

Yield = 15%

F (Tottoli) = 287°C

N.M.R.1H  $\delta$  (ppm) : 1.95 (m. 4H) ; 3.3 (m. 4H) ; 7.3 (s. 2H) ; 7.2 – 7.6 (m. 7H) ; 8.1 (d. 1H) ; 10.2 (s. 1H)

Solvent : DMSO

**Example 220** : 4-(4-cyanobenzyl)-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

1/ Example 220-1/ 1-(pyrrolidin-1-yl)-7-(4-tolylsulfonyloxy)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

1.3g of this compound is obtained from 2.4g of 4-benzyl-1-(pyrrolidin-1-yl)-7-(4-tolylsulfonyloxy)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (example 219-3) by debenzylation method described in example 263.

Yield = 68%

2/ Example 220-2/ 4-(4-cyanobenzyl)-1-(pyrrolidin-1-yl)-7-(4-tolylsulfonyloxy)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.48g of this compound is obtained from 0.66g of 1-(pyrrolidin-1-yl)-7-(4-tolylsulfonyloxy)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (example 220-1) by N-alkylation method described in example 3.

Yield = 52%

3/ Example 220-3/ 4-(4-cyanobenzyl)-7-hydroxy-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.3g (0.55 mmol) of 4-(4-cyanobenzyl)-1-(pyrrolidin-1-yl)-7-(4-tolylsulfonyloxy-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (described in example 220-2) is dissolved in 1ml of dry DMF. We add 0.27ml of pyrrolidine (2.75 mmol) then heat at 140°C, under shaking, for 6 hours. The solvent is evaporated under vacuum and the residue is resuspended by a mixture of ethyl acetate / aqueous N hydrochloric acid solution. The insoluble residue is separated by filtration, washed in water until neutral pH and dried under vacuum ; we obtain 0.13g of crude product, which is crystallized in 5 ml of ethanol, filtered and dried to give 0.085g of pure product.

Yield = 40%

F(Tottoli) = 305°C

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 (m. 4H) ; 3.3 (m. 4H) ; 5.35 (s. 2H) ; 7.35 (d. 1H) ; 7.6 – 7.7 (m. 3H) ; 7.8 (d. 2H) ; 8.1 (d. 1H) ; 10.2 (s. 1H)

Solvent : DMSO

**Example 221 :** 7-acetamido-4-benzyl-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

1/ Example 221-1/ 7-acetamido-4-benzyl-1-bromo -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.45g of this compound is obtained from 0.5g of 7-acetamido-4-benzyl -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one by bromination method which is described in example 256.

Yield = 72 %

2/ Example 221-2/ 7-acetamido-4-benzyl-1-(pyrrolidin-1-yl)- 4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

8.7g (21 mmol) of brominated derived which is obtained in example 221-1 are treated by 3.7 ml (42 mmol) of pyrrolidine and 3.54g (42 mmol) of sodium bicarbonate in 80 ml of DMF in conditions of example 164. After treatment, we obtain 8.0g of crude product which is purified by chromatography on silica column by elution with the mixture  $\text{CH}_2\text{Cl}_2$  98 /  $\text{CH}_3\text{OH}$  2. The fractions containing the pure product are joined and concentrated, then the residue is

crystallized in ethanol to give 6.6g of 7-acetamido-4-benzyl-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

Yield = 78 %

F(Tottoli) = 265°C

5 N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2 – 2.1 (m. 4H) ; 2.25 (s. 3H) ; 3.4 (m. 4H) ; 5.45 (s. 2H) ; 7.2 – 7.3 (m. 3H) ; 7.6 (d. 2H) ; 8.1 (s. 1H) ; 8.2 (m. 2H) ; 8.4 (d. 1H)

Solvent :  $\text{CDCl}_3$

10 **Example 222** : 7-acetamido-4-[(E)-3-phenylallyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

From 1.2g (3.0 mmol) of 7-acetamido-4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (described in example 221) debenzylated in 7-acetamido-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one by Palladium/C method described in example 15 257, then directly treated with 0.59g of cinnamyl bromide in the presence of 0.98g cesium carbonate, in 15 ml of DMF, according to a method described in example 3. We obtain, after purification by chromatography on silica column and recrystallization in ethanol, 0.4g of pure compound from example 222.

Yield = 31 %.

20 F (Tottoli) = 248° C

CCM ( $\text{CH}_2\text{Cl}_2$  95 /  $\text{CH}_3\text{OH}$  5) :  $R_f$  = 0,30

NMR  $^1\text{H}$   $\delta$  (ppm)  $\text{CDCl}_3$  :

2.0-2.1 (m.4H) ; 2.25 (s. 3H) ; 3.45 (m. 4H) ; 5 (d. 2H) ; 6.35-6.4(dt. 1H) ; 6.8 (d. 1H) ; 7.15-7.35 (m. 5H) ; 8.1 (s. 1H) ; 8.2-8.3 (m. 2H) ; 8.4 (m. 1H)

25 **Example 223** : 7-amino-4-[(E)-3-phenylallyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a 20 ml balloon flask, we resuspend 0.2g (0.46 mmol) of 7-acetamido-4-[(E)-3-phenylallyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (described in 30 example 222) in 5 ml of 6N hydrochloric acid solution and heat by reflux, under shaking, for 15 minutes. After cooling down, the obtained solution is alkalized by soda solution, extracted 3 times by methylene chloride. The joined organic phases are washed with a NaCl-













saturated solution, dried on Na<sub>2</sub>SO<sub>4</sub> then evaporated under vacuum. The crude product (0.12g) is recrystallized in ethanol to give 0.08g of the pure compound from example 223.

Yield = 44 %

F (Tottoli) = 199°C

- 5 NMR <sup>1</sup>H δ (ppm) CDCl<sub>3</sub> :  
 2.1 (m. 4H) ; 3.4 (m. 4H) ; 4.0 (m. 2H) ; 5.1 (d. 2H) ; 6.5-6.6 (dt. 1H) ; 6.85 (d. 1H) ; 7.0-7.3 (m. 3H) ; 7.6 (m. 1H) ; 7.7 (m. 1H) ; 8.1 (m. 1H) ; 8.45 (s. 1H) ; 8.6 (s. 1H).
- 10 The general formula (I) compounds of examples 224 to 233 in table5 are prepared by method from example 223.

TABLE 5

N° Compound	X1	R	NR4R5	Yld (%)	MP (°C)
224	7-NH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		40	240 (dec)
225	7-NH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		60	230
226	7-NH <sub>2</sub>	4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		67	152
227	7-NH <sub>2</sub>	(E) (3-pyridyl)-CH=CHCH <sub>2</sub>		70	201
228	7-NH <sub>2</sub>	4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		68	163
229	7-NH <sub>2</sub>	(E) C <sub>6</sub> H <sub>5</sub> CH=CHCH <sub>2</sub>		67	198
230	7-CH <sub>3</sub> NH	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		58	171
231	7-CH <sub>3</sub> NH	4-CNC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		91	270
232	8-CH <sub>3</sub> NH	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		76	-
233	7-C <sub>2</sub> H <sub>5</sub> NH	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>		67	225

**- Compound 224 :**

N.M.R.1H  $\delta$  (ppm) : 1.8 – 1.9 (m. 8H) ; 3.4 – 3.45 (m. 4H) ; 4 (s. 2H) ; 5.4 (s. 2H) ; 7 (m. 1H) ; 7.25 – 7.35 (m. 3H) ; 7.55 (s. 1H) ; 7.65 – 7.80 (m. 2H) ; 8.15 – 8.2 (m. 1H)

Solvent : CDCl<sub>3</sub>

5

**- Compound 225 :**

N.M.R.1H  $\delta$  (ppm) : 2.1 (m. 4H) ; 3.4 (m. 4H) ; 4 (s. 2H) ; 5.45 (s. 2H) ; 7 (d. 1H) ; 7.2 – 7.35 (m. 3H) ; 7.6 (s. 1H) ; 7.7 – 7.8 (d. 2H) ; 8 – 8.1 (d. 1H)

Solvent : CDCl<sub>3</sub>

10

**- Compound 226 :**

N.M.R.1H  $\delta$  (ppm) : 2 - 2.1 (m. 4H) ; 3.35 - 3.45 (m. 4H) ; 4.05 (s. 2H) ; 8.5 (s. 2H) ; 7.05 (m. 1H) ; 7.4 – 7.5 (m. 3H) ; 7.8 (s. 1H) ; 8.05 (d. 1H)

Solvent : CDCl<sub>3</sub>

15

**- Compound 227 :**

N.M.R.1H  $\delta$  (ppm) : 2.1 (m. 4H) ; 3.4 (m. 4H) ; 4 (m. 2H) ; 5.1 (d. 2H) ; 6.4 – 6.5 (dt. 1H) ; 6.9 (d. 1H) ; 7.05 (m. 1H) ; 7.2 – 7.3 (m. 2H) ; 7.35 (d. 2H) ; 7.6 (s. 1H) ; 8.1 (d. 1H)

Solvent : CDCl<sub>3</sub>

20

**- Compound 228 :**

N.M.R.1H  $\delta$  (ppm) : 2.8 (s. 6H) ; 5.4 (s. 2H) ; 5.7 (m. 2H) ; 7.10 – 7.15 (m. 1H) ; 7.4 (s. 1H) ; 7.6 (d. 2H) ; 7.8 (d. 2H) ; 8.05 (d. 1H)

Solvent : DMSO

25

**- Compound 229 :**

N.M.R.1H  $\delta$  (ppm) : 2.9 (s. 6H) ; 4.95 (d. 2H) ; 5.75 (m. 2H) ; 6.45 – 6.5 (dt. 1H) ; 6.7 – 6.8 (d. 1H) ; 7.2 (m. 1H) ; 7.25 – 7.4 (m. 6H) ; 8.1 (d. 1H)

Solvent : DMSO

30

**- Compound 230 :**

N.M.R.1H  $\delta$  (ppm) : 2.1 (m. 4H) ; 2.95 (s. 3H) ; 3.4 (m. 4H) ; 4.1 (m. 1H) ; 5.4 (s. 2H) ; 6.95 (d. 1H) ; 7.3 (m. 3H) ; 7.45 (s. 1H) ; 7.75 (dd. 2H) ; 8.1 (d. 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 231 :**

N.M.R.<sup>1</sup>H δ (ppm) : 2.1 (m. 4H) ; 2.9 (s. 3H) ; 3.4 (m. 4H) ; 5.5 (s. 2H) ; 7 (m. 1H) ; 7.45 (s. 1H) ; 7.6 (m. 2H) ; 7.8 (m. 2H) ; 8.1 (d. 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 232 :**

N.M.R.<sup>1</sup>H δ (ppm) : 1.9 - 2 (m. 4H) ; 2.85 (d. 3H) ; 3.3 (m. 4H) ; 5.3 (s. 2H) ; 6.7 (d. 1H) ; 7.2 (q. 1H) ; 7.25 - 7.45 (m. 6H) ; 7.9 (d. 1H)

Solvent : DMSO

**- Compound 233 :**

N.M.R.<sup>1</sup>H δ (ppm) : 1.3 (t. 3H) ; 2.1 (m. 4H) ; 3.25 (m. 2H) ; 3.4 (m. 4H) ; 3.9 (m. 1H) ; 5.45 (s. 2H) ; 7 (m. 1H) ; 7.2 - 7.3 (m. 3H) ; 7.45 (s. 1H) ; 7.7 (m. 2H) ; 8.1 (d. 1H)

Solvent : CDCl<sub>3</sub>

**Example 234 :** 4-benzyl-7-(N-isopropylamino)-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one

In a 20 ml balloon flask, we resuspend 0.31g (0.86 mmol) of 7-amino-4-benzyl-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (described in example 225) in 10 ml of methylene chloride. We add 0.14 ml (1.9 mmol) of acetone, 0.115 ml (1.9 mmol) of pure acetic acid then 0.546g (2.6 mmol) of sodium triacetoxyborohydrid. The mixture is shaken for 48 hours at ambient temperature, under nitrogen atmosphere. The solvent is evaporated under vacuum and the residue is resuspended in ethyl acetate. The organic phase is washed in a sodium bicarbonate solution, then in NaCl-saturated solution. After drying on Na<sub>2</sub>SO<sub>4</sub> and solvent elimination under vacuum, we obtain 0.3g of crude product which is purified by chromatography on silica column, after elution with mixture CH<sub>2</sub>Cl<sub>2</sub> 98 / CH<sub>3</sub>OH 2 to give 0.2g of pure by CCM compound from example 234.

Yield = 58%

F(Tottoli) = 208°C [EtOH]

N.M.R.<sup>1</sup>H δ (ppm) : 1.2 (m. 6H) ; 2.05 (m. 4H) ; 3.4 (m. 4H) ; 3.7 - 3.85 (m. 2H) ; 5.5 (s. 2H) ; 6.9 (m. 1H) ; 7.2 - 7.3 (m. 3H) ; 7.4 (s. 1H) ; 7.7 (m. 2H) ; 8.1 (m. 1H)

Solvent :  $\text{CDCl}_3$

**Example 235:** 4-benzyl-7-methylsulfonylamino-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one and **example 247** : 4-benzyl-7-(N,N-dimethylsulfonylamino)-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a 20 ml balloon flask, we resuspend 0.55g (1,5 mmol) of 7-amino-4-benzyl-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (described in example 225) in 10 ml of methylene chloride. We add 0.42 ml (3.0 mmol) of triethylamine then 0.24 ml (3.0 mmol) of methanesulfonyl chloride. The obtained solution is shaken for 24 hours at ambient temperature. After cooling down, the obtained solution is washed in water, dried on  $\text{Na}_2\text{SO}_4$  then evaporated under vacuum. The crude mixture of the 2 obtained compounds (0.85g) is chromatographed on silica column by elution with the mixture  $\text{CH}_2\text{Cl}_2$  99 /  $\text{CH}_3\text{OH}$  1 /  $\text{NH}_4\text{OH}$  0.1. The fractions containing the first product by elution order are joined and evaporated under vacuum to give 0.65g of 4-benzyl-7-(N,N-dimethylsulfonylamino)-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

F (Tottoli) =  $221^\circ\text{C}$

N.M.R.  $^1\text{H}$   $\delta$  (ppm) DMSO : 2.2 – 2.3 (m. 4H) ; 2.9 (s. 3H) ; 3.15 (m. 4H) ; 5.15 (s. 2H) ; 7.1 – 7.2 (m. 3H) ; 7.25 (m. 2H) ; 7.5 – 7.6 (d. 1H) ; 7.85 (s. 1H) ; 8.05 – 8.1 (d. 1H) ; 10.05 (s. 1H)

The fractions containing the second product by elution order are treated in a similar manner to give 0.15g of 4-benzyl-7-methylsulfonylamino-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

Yield = 23%

F(Tottoli) =  $283^\circ\text{C}$  [EtOH]

N.M.R.  $^1\text{H}$   $\delta$  (ppm) DMSO : 2 (m. 4H) ; 3.45 (m. 4H) ; 3.5 (s. 3H) ; 5.45 (s. 2H) ; 7.3 (m. 3H) ; 7.7 (m. 3H) ; 6.35 (m. 2H)

**Example 236** : 7-(N,N-dimethylamino)-4-benzyl-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a balloon flask, we resuspend 0.75g (2.05 mmol) of 7-amino-4-benzyl-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (described in example 225) in 0.8 ml of formic acid and 0.8 ml of formol. Under shaking, the mixture is heated at  $100^\circ\text{C}$  for 1 hour. After cooling down, the obtained solution is poured into iced water, the suspension is extracted

several times with ethyl acetate ; the joined organic phases are washed in a aqueous NaCl-saturated solution, dried on Na<sub>2</sub>SO<sub>4</sub> then concentrated under vacuum.

The obtained crude product (0.8g) is purified by chromatography on silica column by elution with methylene mixture chloride 98 / methanol 2. We obtain 0.23g of pure by CCM product from example 236.

Yield = 29%

F (Tottoli) = 194°C [EtOH]

CCM (CH<sub>2</sub> Cl<sub>2</sub> 97 / CH<sub>3</sub> OH 3) : Rf = 0,65

N.M.R.1H δ (ppm) : 2.1 (m. 4H) ; 3.05 (s. 6H) ; 3.45 (m. 4H) ; 5.45 (s. 2H) ; 7.1 (m. 1H) ; 7.3 (m. 3H) ; 7.6 (d. 1H) ; 7.75 (m. 2H) ; 8.1 (d. 1H)

Solvent : CDCl<sub>3</sub>

**Example 237 :** 4-benzyl-7-cyano-1-(N,N-dimethylamino)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a 500 ml balloon flask, equipped with a shaker, refrigeration and nitrogen feeding, we add 10.8g (27,1 mmol) of 4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (example 164) in 100ml of N-methylpyrrolidinone (NMP). We add 4.4g (49 mmol) of cuprous cyanide then heat the mixture, under shaking and under nitrogen for 12 hours. The solvent is eliminated by evaporation under vacuum ; the residue is stirred in mixture of methylene chloride and 2N ammonia solution, the insoluble residue is eliminated by filtration, then the phases are separated by decantation. The organic phase is washed in a NaCl-saturated solution, dried on Na<sub>2</sub>SO<sub>4</sub> and evaporated to give 24.0g of crude product. This is purified by chromatography on silica column by elution using mixture of ethyl acetate 65 / cyclohexane 35. The fractions pure in CCM are joined and evaporated under vacuum : we obtain 8.4g of compound from example 237.

Yield = 90%.

F (Tottoli) = 212-214°C

N.M.R.1H δ (ppm) : 2.9 (s. 6H) ; 5.3 (s. 2H) ; 7.3 (m. 3H) ; 7.5 (m. 2H) ; 8.4 (m. 1H) ; 8.5 (m. 1H) ; 8.6 (m. 1H)

Solvent : DMSO

**Example 238 :** 4-benzyl-7-carboxy-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

In a 250ml balloon flask, we add 5.0 g (13,5 mmol) of 4-benzyl-7-cyano-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one in 100ml of 16 N hydrochloric acid solution then heat by reflux for 3 hours, under shaking.

After cooling down, the precipitate is filtered, washed several times in water, dried and purified by chromatography on silica column, by elution with the mixture CH<sub>2</sub>Cl<sub>2</sub> 97 / CH<sub>3</sub>OH 3, to give 2,3g of pure by CCM compound from example 238.

Yield = 44%

F(Tottoli) = 335-337°C

N.M.R.1H δ (ppm) : 1.9 (s. 4H) ; 3.4 (s. 4H) ; 5.3 (s. 2H) ; 7.3 (m. 3H) ; 7.4 (m. 2H) ; 8.2 (m. 1H) ; 8.4 (m. 1H) ; 8.7 (s. 1H)

Solvent : DMSO

**Example 239 :** 7-bromo-4-[(4-methoxycarbonylmethyl)benzyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.8g (1,65 mmol) of 7-bromo-4-[(4-carboxymethyl)benzyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (example 56) and 0.25g of potassium carbonate are resuspended in 10 ml of DMF. We add 0.26g (1.82 mmol) of methyl iodide then heat at 80°C, under shaking, for 2 hours. The solvent is evaporated under vacuum, the residue is resuspended in water, this latter being extracted 3 times by ethyl acetate; the joined organic phases are washed in sodium chloride saturated solution, dried on Na<sub>2</sub>SO<sub>4</sub> then the solvent is evaporated under vacuum to give 0.7g of crude product.

This is purified by chromatography on silica column by elution with mixture CH<sub>2</sub>Cl<sub>2</sub> 99 / CH<sub>3</sub>OH 1. We obtain 0.5g of pure by CCM product.

Yield = 61 %

F(Tottoli) = 161-162°C [C<sub>2</sub>H<sub>5</sub>OH]

N.M.R.1H δ (ppm) : 2 - 2.1 (m. 4H) ; 3.35 – 3.45 (m. 4H) ; 3.6 (s. 2H) ; 3.7 (s. 3H) ; 5.45 (s. 2H) ; 7.2 (d. 2H) ; 7.65 (d. 2H) ; 7.85 (d. 1H) ; 8.15 (d. 1H) ; 8.5 (s. 1H)

Solvent : CDCl<sub>3</sub>

**Example 240 :** 7-bromo-4-[(4-(N-methylcarbamoyl)methyl)benzyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

240-1/ 7-bromo-4-[(4-chloroformylmethyl)benzyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

0.85g (1,76 mmol) of 7-bromo-4-[(4-carboxymethyl)benzyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one (example XX) is added in 85 ml of dry chloroform. Under nitrogen feeding, we shake then add 0.42g (3.52 mmol) of thionyl chloride maintaining temperature below 5°C. After 90 minutes, the reaction is almost complete and chloride acid tends to precipitate as crystal. This solution will be used like in the next step.

240-2/ 7-bromo-4-[(4-(N-methylcarbamoyl)methyl)benzyl]-1-(pyrrolidin-1-yl) -4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one.

To the solution cooled down at 0°C of 0.6g (8.8 mmol) of methylamine chlorhydrate and 1.06g of triethylamine in 85 ml of acetone, we add slowly the obtained solution from example 240-1, maintaining temperature below 5°C. Shaking is then maintained at 0°C for 15 minutes then the obtained solution is concentrated under vacuum. We dissolve the residue in methylene chloride, wash the organic phase twice in water, dry on Na<sub>2</sub>SO<sub>4</sub>, evaporate the solvent under vacuum and recover then 1.0g of crude product. This is chromatographed on silica column by elution using mixture CH<sub>2</sub>Cl<sub>2</sub> 96 / CH<sub>3</sub>OH 4 to give 0.4g which is recrystallized in ethanol. We obtain 0.27g of pure compound after drying.

Yield = 31 %

F (Tottoli) = 240°C




CCM (CH<sub>2</sub> Cl<sub>2</sub> 92 / CH<sub>3</sub> OH 8) : R<sub>f</sub> = 0.5

N.M.R.1H δ (ppm) : 1.95 - 2.1 (m. 4H) ; 2.7 (d. 3H) ; 3.35 - 3.45 (m. 4H) ; 3.5 (s. 2H) ; 5.3 - 5.5 (m. 3H) ; 7.15 (d. 2H) ; 7.65 (d. 2H) ; 7.9 (d. 1H) ; 8.2 (d. 1H) ; 8.5 (s. 1H)

Solvent : CDCl<sub>3</sub>

The compounds (I) from examples 241 to 243 (table6) are prepared according to process in example 240.

TABLE 6

N° Compound	R	NR <sub>4</sub> R <sub>5</sub>	Yld (%)	MP (°C)
241	4-(NH <sub>2</sub> COCH <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		38	268
242	4-(Me <sub>2</sub> NCOCH <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		74	202
243	4-(HONHCOCH <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>		47	229

**- Compound 241 :**

N.M.R. <sup>1</sup>H δ (ppm) : 2.7 (s. 6H) ; 3.2 (s. 2H) ; 5.1 (s. 2H) ; 6.7 (s. 1H) ; 7.05 (d. 2H) ; 7.2 (m. 3H) ; 7.95 (m. 1H) ; 8.05 (d. 1H) ; 8.15 (s. 1H)

Solvent : DMSO

**- Compound 242 :**

N.M.R. <sup>1</sup>H δ (ppm) : 2 - 2.15 (m. 4H) ; 2.9 (s. 3H) ; 2.95 (s. 3H) ; 3.35 – 3.45 (m. 4H) ; 3.7 (s. 2H) ; 5.45 (s. 2H) ; 7.15 (d. 2H) ; 7.65 (d. 2H) ; 7.85 (d. 1H) ; 8.15 (d. 1H) ; 8.5 (s. 1H)

Solvent : CDCl<sub>3</sub>

**- Compound 243 :**

N.M.R. <sup>1</sup>H δ (ppm) : 1.95 - 2.1 (m. 4H) ; 3.3 (s. 2H) ; 3.3 – 3.4 (m. 4H) ; 5.3 (s. 2H) ; 7.25 (d. 2H) ; 7.45 (d. 2H) ; 8.15 (d. 1H) ; 8.25 (d. 1H) ; 8.35 (s. 1H) ; 8.8 (s. 1H) ; 10.7 (s. 1H)

Solvent : DMSO

**Example 244** : 7-methyl-4-(4-cyanobenzyl-1-(N,N-dimethylamino)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-thione.

244-1/ 7-methyl-1-(N,N-dimethylamino)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-thione.

In a three-necked balloon flask equipped with shaker, refrigeration and nitrogen feeding, we add 1.0g (4,1 mmol) of 7-methyl-1-(N,N-dimethylamino)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one in 70 ml of toluene and add at once 3.3g (8.2 mmol) of Lawesson's reagent.



Under shaking, the mixture is heated by reflux for 24 hours. After cooling down, we add 30 ml of 5% hydrochloric acid solution, then we pour in 250 ml of methanol under shaking. We add 250 ml of cyclohexane and we eliminate the insoluble residue by filtration. The methanolic acid phase is separated by decantation, concentrated under vacuum and the residue is resuspended in ice and is triturated several times. The insoluble residue recovered as a resin is dissolved in 10 ml of isopropanol; from the obtained solution, shaken for 30 minutes, the yellow crystals which have precipitated are filtered, washed in isopropanol then in ether and dried under vacuum. We obtain 0.98g of product that will be used like this in the next step.

Yield = 80 %

244-2/ 4-(4-cyanobenzyl)-1-(N,N-dimethylamino)-7-methyl-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-thione.

From 0.5g (1.93 mmol) of 7-methyl-1-(N,N-dimethylamino)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-thione (example 244-2), by using method B described in example 3, we obtain, after recrystallization in ethanol, 0.29g of compound from example 244.

Yield = 40 %

F(Tottoli) = 236°C

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.9(s.6H) ; 3.7(s.2H) ; 5.45(s.2H) ; 7.25(m.2H) ; 7.7(m.2H) ; 7.85(m.1H) ; 8.2(d.1H) ; 8.5(s.1H)

Solvent :  $\text{CDCl}_3$

The compounds (I) of examples 245 to 246 (table7) are prepared according to process in example 244.

TABLE 7

N°. Compound	X1	R	NR4R5	Yld (%)	MP (°C)
245	7-Br	4-CNC6H4CH2	$\begin{array}{c} \text{CH}_3 \\   \\ \text{N} \\   \\ \text{CH}_3 \end{array}$	13	276
246	7-CH3	(E) (pyridin-3-yl)-CH=CHCH2	$\begin{array}{c} \text{CH}_3 \\   \\ \text{N} \\   \\ \text{CH}_3 \end{array}$	26	133

**- Compound 245 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.9 (s. 6H) ; 4.7 (s. 2H) ; 7.65 (d. 2H) ; 7.75 (d. 2H) ; 8.1 (m. 2H) ; 8.4 (d. 1H)

Solvent : DMSO

**- Compound 246 :**

N.M.R.  $^1\text{H}$   $\delta$  (ppm) : 2.5 (s. 3H) ; 3.0 (s. 6H) ; 4.25 (d. 2H) ; 6.45 (dt. 1H) ; 6.75 (d. 1H) ; 7.2 (m. 1H) ; 7.6 (d. 1H) ; 7.7 (d. 1H) ; 7.9 (s. 1H) ; 8.4 (m. 2H) ; 8.6 (bs. 1H)

Solvent :  $\text{CDCl}_3$

**B. Intermediate compounds**

Particularly preferred intermediate compounds of the current invention may be prepared according to the following examples. However, the person skilled in the art may modify easily operative procedures described below depending on the desired intermediate.

**Example 250**

**Intermediate 1 :**

1,2,3,4-tetrahydro-3-benzyl-6-bromo-4-oxo-2-thia-quinazoline from 5-bromo anthranilic acid.

In a reactor equipped with shaker, refrigeration and bromide funnel, 150 g (694 mmol) of 5-bromo-2-amino-benzoic acid are resuspended in 1.5 l of acetic acid.

Under shaking, the mixture is heated by reflux, then 92 ml (103 g ; 694 mmol) of benzyl isothiocyanate are added slowly and regularly using the bromide funnel.

After addition, shaking and heating by reflux are maintained for 6 hours, solubilization is realized gradually during this period.

After cooling down to ambient temperature, the solid that has precipitated is filtered and washed in acetic acid.

The product obtained is dried under vacuum at 60° C to give 125.2 g of expected pure by CCM compound (elution solvent:  $\text{CH}_2\text{Cl}_2$  99.2 /  $\text{CH}_3\text{OH}$  0.8 ;  $R_f$  = 0.9)

Yield = 52 %

NMR  $^1\text{H}$  and  $^{13}\text{C}$  spectra are compatible with the expected structure.

### Example 251

#### Intermediate 2:

3, 4-Dihydro-3-benzyl-6-bromo-2-hydrazino-quinazolin-4-one.

In a reactor equipped with shaker, refrigeration, 125.2 g (360 mmol) of 1,2,3,4-tetrahydro-3-benzyl-6-bromo-4-oxo-2-thia-quinazoline (Intermediate 1) are added in 3.5 l of ethanol.

Under shaking, we add 167.6 g (3.348 mmol) of hydrazine hydrate.

The obtained suspension is heated by reflux for 18 hours, during which solubilization is gradually realized.

After cooling down to ambient temperature, about half of solvent is evaporated under vacuum and the obtained residual solution is left aside in a ice bath for 1 hour.

After filtration of the precipitate, cold ethanol wash then drying under vacuum at 60° C, we obtain 89.7 g of expected pure by CCM compound, (elution solvent: CH<sub>2</sub>Cl<sub>2</sub> 99 / CH<sub>3</sub>OH 1 ; R<sub>f</sub> = 0.1)

Yield = 72 %

NMR <sup>1</sup>H and <sup>13</sup>C spectra are compatible with the expected structure.

### Example 252

#### Intermediate 3 :

4-benzyl-7-chloro-1-mercapto-4H-[1,2,4] triazolo [4, 3-a] quinazoline -5-one

In a reactor equipped with shaker and refrigeration, we resuspend 47.7 g (158 mmol) of 3,4-dihydro-3-benzyl-6-chloro-2-hydrazino-quinazolin-4-one (prepared in a similar manner as intermediate 2) in 600 ml of pyridine.

We add then 25.3 g (158 mmol) of potassium xanthogenate by fraction, the obtained solution is heated by reflux for 7 hours, under shaking, during which the solid is gradually precipitated.

After one night's rest at ambient temperature, the precipitate is separated by filtration then redissolved in 1.5 l of water.

The obtained solution is neutralized by acid acetic, then the formed precipitate is filtered, washed in water until neutral pH and dried.

We obtain 54.0 g of crude product which will be used like this in the next step.

Yield ≈ 100 %

### Example 253

#### Intermediate 4 :

5 4-benzyl-7-chloro-1-méthylthio-4H-[1,2,4] triazolo [4, 3-a] quinazolin-5-one.

In a reactor equipped with a shaker and bromide funnel, we resuspend 6.72g of soda in 1200 ml of water then add 57.0 g (166 mmol) of 4-benzyl-7-chloro-1-mercapto-triazolo [4, 3-a] quinazolin-5-one (Intermediate 3).

10 Under shaking, we add 15.74 ml (166 mmol) of dimethyl sulfate at ambient temperature, over a 30 minutes period. Shaking is maintained for 7 hours.

After leaving aside at ambient temperature for a night, the precipitate is filtered, washed in water then dried under vacuum.

We obtain 51.2 g of crude solid which is used like this in the next step.

15 Yield = 100%

### Example 254

#### Intermediate 5 : 4-benzyl-1,7-dichloro-4H-[1,2,4] triazolo [4, 3-a] quinazolin-5-one.

20 In a reactor equipped with shaker, plunging tube and refrigeration, we add 51.0 g (143 mmol) of 4-benzyl-7-chloro-1-méthylthio-triazolo [4, 3-a] quinazolin-5-one (Intermediate 4) in a mixture of 1.5 l of chloroform and 0.9 l of water.

Under shaking, we cool down to 0° C, then allow a chlorine stream to flow, maintaining temperature below 10° C for 2 hours.

25 We then stop chlorine feeding, leave the mixture to return to ambient temperature then maintain shaking for 2 hours.

The 2 phases are separated by decantation, the chloroformic phase is dried on Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum .

30 We obtain 50.9 g of crude solid residue. This is resuspended in 400 ml of ethanol and the heterogeneous mixture is shaken for 30 minutes. The insoluble residue is filtered, washed in ethanol and dried at 50° C under vacuum to give 46.5 g of pure expected by CCM compound (elution solvent: CH<sub>2</sub>Cl<sub>2</sub> 99 / CH<sub>3</sub>OH 1 ; R<sub>f</sub> = 0.50)

Yield = 94 %

Proton and <sup>13</sup>C NMR spectra are compatible with the expected structure.

### Example 255

5 **Intermediate 6**: 4-benzyl-7-bromo-4H-[1,2,4] triazolo [4, 3-a] quinazolin-5-one.

In a 6 liter reactor, equipped with shaker, we add 89.7 g (260 mmol) of 3,4-dihydro-3-benzyl-6-bromo-2-hydrazino-quinazolin-4-one (Intermediate 2) in 2.9 l of dry chloroform.

10 We shake, cool the suspension down to 0° C using an ice bath, then add 216 ml (192.5 g; 1.299 mmol) of triethyl orthoformate, leading to a slight temperature increase (up to 6° C).

Maintaining the temperature below 5° C, we add 8.2 ml of concentrated sulfuric acid in a single go. We shake then for 15 min at temperature below 5° C, then remove the ice bath, shaking is maintained for 4 additional hours during which a solid gradually precipitates.

15 We add 1.5 l of water and 0.7 l of chloroform, shake until complete distribution between the 2 phases then neutralize the aqueous phase to pH 7 by sodium bicarbonate.

The organic phase is decanted, washed with NaCl-saturated solution, dried on Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum to give 91.3 g of expected pure by CCM compound, (elution solvent: CH<sub>2</sub>Cl<sub>2</sub> 97 / CH<sub>3</sub>OH 3 / NH<sub>4</sub>OH 0,3 ; R<sub>f</sub> = 0.5).

Yield = 99 %

20 PF (Tottoli) = 237° C

NMR <sup>1</sup>H and <sup>13</sup>C spectra are compatible with the expected structure.

### Example 256

#### **Intermediate 7**:

25 4-benzyl-1, 7-dibromo-4H-[1,2,4] triazolo [4, 3-a] quinazolin-5-one.

In a 3 liter reactor equipped with shaker, refrigeration and bromide funnel, we add 35 g (98.5 mmol) of 4-benzyl-7-bromo-4H-[1,2,4] triazolo [4,3-a]quinazoline-5-one (Intermediate 6) in 630 ml of chloroform and 11 ml of pyridine.

30 Under shaking, 16.4 ml (320 mmol) of bromine are then added at ambient temperature over a 30 minute period.

After addition, shaking is maintained at ambient temperature for 1 hour ; the reaction medium is then distributed between 1 l of water and 1.5 l of chloroform and the heterogeneous mixture shaken for 15 min.

The insoluble residue is dried, washed in water to a neutral pH then triturated in ethanol.

After drying under vacuum at 50 ° C, we obtain a first fraction of 8.2 g of pure by CCM expected compound (elution solvent : CH<sub>2</sub>Cl<sub>2</sub> 99 / CH<sub>3</sub>OH 1 ; R<sub>f</sub> = 0.6).

After separation of the chloroformic phase, washing in sodium bicarbonate solution then in water, drying on Na<sub>2</sub>SO<sub>4</sub>, evaporation of solvent under vacuum then triturating of residue in ethanol, filtration and drying of solid at 50° C, we obtain 33.1 g of a second fraction of expected compound, equivalent by CCM to the precedent fraction.

Yield total (of the 2 fractions) = 96%

NMR <sup>1</sup>H spectrum is compatible with the expected structure.

#### Example 257

#### Intermediate 8: 1-Azepanyl-4H-[1,2,4] triazolo[4,3-a] quinazolin-5-one

In a 150 ml balloon flask equipped with shaker and refrigeration , we dissolve 1.0 g (2.68 mmol) of 1-Azepanyl-4-benzyl-4H-[1,2,4] triazolo[4,3-a] quinazolin-5-one in 60 ml of tetrahydrofuran.

We add 2.0 g of ammonium formate then 1.5 g of 10 % activated palladium on charcoal.

The mixture is shaken and heated by solvent reflux for 5 hours.

After cooling down, the suspension is filtered, and then the solvent is evaporated under vacuum to give 0.55 g of residual solid.

This is chromatographed on silica column by elution using mixture CH<sub>2</sub> Cl<sub>2</sub> 97 / CH<sub>3</sub> OH 3 ; the fractions pure in CCM are gathered together and concentrated under vacuum to give 0,42 g of residual solid.

Yield = 55%

F (Tottoli) = 222 – 224°C







CCM (CH<sub>2</sub> Cl<sub>2</sub> 95 / CH<sub>3</sub> OH 5) : R<sub>f</sub> = 0,4

N.M.R. <sup>1</sup>H δ (ppm) : 1.65-1.85 (m. 8H) ; 3.25 (m. 4H) ; 7.5 (t.1H) ; 7.9 (t. 1H) ; 8.15 (d. 1H) ; 8.3 (d.1H) ; 12.6 (m. 1H)

Solvent : DMSO

The compounds (I ; R = H) of examples 258 to 262 (table8) are prepared according to the process in example 257.

TABLE 8

N. Compound	X1	NR4R5	Yld (%)	MP (°C)
258	7-Br		96	>290
259	8-CH3		64	-
260	8- 		75	-
261	7-Br		89	>300
262	7-Br		90,5	>300

## Example 263

**Intermediate 9** : 1-Azepanyl-7-chloro-4H-[1,2,4] triazolo[4,3-a] quinazolin-5-one

10.0 g of 1-Azepanyl-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one (24,5mmol) then 19.6 g (147 mmol) of dry aluminium chloride are resuspended in 200 ml of anhydrous benzene.

The suspension is shaken and heated at 50° C in the absence of humidity.

After 90 minutes, we allow to cool down, add some ice to the reaction mixture then shake the mixture vigorously for 30 minutes.

The obtained precipitate is dried, washed in water to a neutral pH and dried at 50°C to give 7.5 g of pure by CCM solid.








Yield = 96 %

F (Tottoli) : >300°C

CCM (CH<sub>2</sub> Cl<sub>2</sub> 95 / CH<sub>3</sub> OH 5) : R<sub>f</sub> = 0.35

N.M.R. <sup>1</sup>H δ (ppm) : 1.65-1.9 (m. 8H) ; 3.3 (m. 4H) ; 7.95 (d. 1H) ; 8.05 (s. 1H) ; 8.3 (d. 1H) ; 12.8 (m.1H)

TABLE 9

N° Compound	X1	NR4R5	MP (°C)
264	H		283
265	7-CH3		298
266	7-CH3		>300
267	7-CH3		-
268	7-OH		295
269	7-CN		>300
270	7-CN		-

## 5 Example 271

**Intermediate 10** : 1-amino-4-benzyl-7-bromo-4H-[1,2,4] triazolo[4,3-a] quinazolin-5-one

In a 500ml reactor equipped with shaker, refrigeration equipped with a potash keeper, thermometer and nitrogen feeding, we resuspend 5.0g (14.5 mmol) of 3, 4-dihydro-3-benzyl-6-bromo-2-hydrazino-quinazolin-4-one (prepared according example XX) in 150 ml of dry methanol. We add 1.62g (15.3 mmol) of cyanogene bromide and shake the heterogeneous mixture for 1 hour at ambient temperature, then by reflux for 5 hours After cooling down, we add drop by drop, under vigorous shaking, aqueous solution of saturated sodium bicarbonate to pH 8. The insoluble solid is filtered, washed several times in water and dried under vacuum to give 4.9g of crude product.



The latter is triturated in 100 ml of methanol, the insoluble fraction is separated by filtration, washed in methanol and dried under vacuum. We obtain 4.6g of pure by CCM product. NMR  $^1\text{H}$  and  $^{13}\text{C}$  spectra are compatible with the expected structure.

Yield = 86.5 %

5 F (Tottoli) = 287°C

CCM ( $\text{CH}_2 \text{Cl}_2$  95 /  $\text{CH}_3 \text{OH}$  5) : Rf = 0.5

### Evaluation of *in vitro* activity of the preferred compounds of the invention

#### **Inhibition of the phosphodiesterase**

The capacity of the formula (I) compounds of the invention to inhibit the cyclic nucleotide phosphodiesterases is evaluated by their  $\text{CI}_{50}$  measurement (necessary concentration to inhibit 50 % of enzymatic activity).

The type 4 phosphodiesterases are obtained from a cytosolic preparation extracted from the human origin cellular line U937 according to a method adapted from T.J. Torphy and al., 1992, J.Pharm.Exp. Ther. 263 : 1195-1205

The other classes of phosphodiesterases are obtained after partial purification FPLC on Mono Q column. (anion exchange column) according to a method adapted from **Lavan B. E., Lakey T., Houslay M. D.** Biochemical Pharmacology, 1989, 38(22), 4123-4136., and from **Silver P.J and al.**, 1988, Eur.J. Pharmacol. 150 : 85-94, either, from human origin cellular lines for PDE 1 (monocytar line TPH1) and PDE5 (line MCF7 issued from an adenocarcinoma), or from dog aorta for PDE 3, or for the human PDE3A, from gene cloning in insect cells SF21 in baculovirus, according to a method adapted from Luckow, V. A. and al., 1991 in Recombinant DNA Technology&Applications.,eds. Prokop, Bajpai,R.K.&Ho,C.S., pp97-152. The enzymatic activity measurement of the different PDE classes, and in particular the PDE 4, is performed according to a method adapted from W.J. Thompson and al. 1979, Advances in Cyclic Nucleotide Research, Vol. 10 : 69-92, ed. G. Brooker and al. Raven Press, NY.

For the  $\text{CI}_{50}$  determination, the enzymatic activity is measured in the presence of inhibitor within concentration margins of 0.1 to 100 $\mu\text{M}$ .

The following table illustrates the PDE4 inhibitory activity from enzymatic preparation obtained from the line U937.

N° Compound	IC <sub>50</sub> (μM)	N° compound	IC <sub>50</sub> (μM)	N° compound	IC <sub>50</sub> (μM)
1	0.054	59	0.090	190	0.19
3	0.079	60	0.050	218	0.048
11	0.080	61	0.011	223	0.012
13	0.060	62	0.053	224	0.075
20	0.04	75	0.078	227	0.028
22	0.41	76	0.070	229	0.080
32	0.053	78	0.038	230	0.002
34	0.056	79	0.14	231	0.00027
35	0.020	80	0.073	233	0.18
37	0.015	81	0.016	234	2.69
40	0.014	83	0.012	239	0.005
41	0.018	85	0.041	240	0.013
42	0.024	89	0.027	242	0.011
43	0.030	92	0.030	243	0.028
44	0.090	94	0.029	246	0.041
46	0.090	96	0.058		
47	0.050	98	0.029		
48	0.025	102	0.060		
49	0.080	103	0.039		
50	0.035	104	0.077		
51	0.027	164	0.090		
52	0.030	186	0.090		
57	0.014	189	0.078		

The examination of the results from the above table shows that the preferred products of the invention tested in the trial inhibit the enzyme PDE4 in vitro in an efficient manner.

### Inhibition of TNF $\alpha$ production by human leukocytes stimulated by lipopolysaccharid

This test aims to evaluate capacity of the compounds of the invention to inhibit TNF $\alpha$  (tumor necrosis- $\alpha$ ) production by human leukocytes in the presence of high human serum concentration (75%). Indeed, it appears that a number of compounds having a capacity any longer to inhibit phosphodiesterase 4 in enzymatic or cellular tests do not present anymore this capacity when the test is performed in human blood. The test described here is based on the use of human leukocytes cultivated in 75% of human serum. It had been previously documented that these conditions simulate the observed situation when TNF $\alpha$  dosage is performed in human blood.

The compounds to test are dissolved into 20 mM (sometimes 6 mM) of DMSO. 100  $\mu$ l of DMSO are distributed into 7 wells of a 96 well microtiter plate (wells B to H). 150  $\mu$ l of the compound solution are distributed into line A wells. 50  $\mu$ l are then sequentially transferred 7 times. 20  $\mu$ l of this serial dilutions of compounds are sequentially transferred twice in wells containing 180  $\mu$ l of RPMI 1640 (Gibco). 50  $\mu$ l of these dilutions are then transferred in wells where cells will be added.

Each test includes a series of eight wells without LPS (100% of inhibition), eight wells with LPS (0% of inhibition) and a series of Rolipram dilutions in order to enable comparison of the tests between each other and then to evaluate their variability.

A leukocyte vial is unfrozen in bain-marie (37°C), its content is transferred into a 15 ml tube containing 10 ml of RPMI added with 5% of human serum (RPMI-5% HS). The cells are sedimented (800 g, 6 minutes, 4°C), resuspended in 10 ml of the same medium and counted by dilution in Trypan blue solution. After centrifugating (800 g, 6 minutes, 4°C), the cells are resuspended to  $2 \times 10^6$ /ml in human serum.

To 50  $\mu$ l aliquots of different dilutions of compounds, 100  $\mu$ l of cells are added. The plates are then incubated 30 minutes at 37°C, then 50  $\mu$ l of solution 4  $\mu$ g/ml of LPS prepared in human serum are added. The plates are incubated for the night at 37°C.

After incubation for 15-18 hours, 90  $\mu$ l of growth supernatant are taken and transferred into rounded-bottom microtiter wells. The TNF $\alpha$  presence is then evaluated by ELISA (Pharmingen) by using 50  $\mu$ l of supernatant. The protocol described by the manufacturer is strictly applied.

Results obtained for some of the preferred compounds of the current invention are illustrated in the following table.

Compound	Inhibition (human leukocytes) IC <sub>50</sub> μM
3	3.4
104	8.1
94	6.3
101	8.6
85	6.8
98	-
79	5.2
91	-
93	4.3
103	10.7
46	-
35	-

## **Evaluation of *in vivo* activity of compounds of the invention**

### ***In vivo* TNF $\alpha$ model in Wistar rat**

The TNF $\alpha$  is a cytokin playing a central role in inflammation mechanisms. Its production may be induced by injection of lipopolysaccharid (LPS). It has been shown that the intracellular AMPc increase, produced in particular by PDE4 inhibitors, decreases the TNF $\alpha$  production in *in vitro* and *in vivo* models. Therefore it matters here to quantify *in vivo* anti-inflammatory potential of the compounds of the invention, administrated by oral route (p.o.) by measuring inhibition of TNF $\alpha$  production in plasma in rat, the latter having received a intraperitoneal injection (i.p.) of lipopolysaccharid (LPS). The treatment by the compounds of the invention or the carrier is administrated by oral route in male Wistar rats, 30 min. before LPS injection. The rats are sacrificed 90 min. after LPS stimulation, the blood is harvested on EDTA and TNF $\alpha$  concentration is measured in each plasma sample. The results obtained from some of the compounds of the current invention are presented in the table below.

Compound	% Inhibition to 10 mg/kg
3	- 98 %
104	- 94 %
94	- 87 %
101	- 80 %
85	- 77 %
98	- 75 %
79	- 72 %
91	- 70 %
93	- 67 %
103	- 64 %
46	- 58 %
35	- 51 %

## References

Chen, Y. L., the Vraux, V., Giroud, J. P. and Chauvelot-Moachon L. (1994). Anti-tumor necrosis factor properties of non-peptide drugs in acute-phase responses. Eur. J. Pharmacol., 271 (2-3), 319-27.

Prabhakar, U., Lipshutz, D., O'Leary Barthus, J., Slivjak, J., Smith III E. F., Lee, J. C. and Esser K. M. (1994). Characterization of cAMP-dependent inhibition of LPS-induced TNF $\alpha$  production by rolipram, a specific phosphodiesterase IV (PDE IV) inhibitor. Int. J. Immunopharmacol., 16 (10), 805-816.

## **Model of eosinophily in rat**

The studies undertaken from this experimental model aim to evaluate inhibitory effect of the compounds of the invention on the rush of inflammatory cells and in particular of eosinophils in the opening of trachea-bronchial shaft in rat. The eosinophils play a major role in asthma physiopathology in human by releasing on the level of pulmonary parenchyma some pro-inflammatory mediators like leukotriens, proteins and specific enzymes (ECP, EPO, MBP) and cytokins. The massive recruitment of this cellular type air passages in asthmatic patient leads to a progressive degradation of pulmonary tissue explaining bronchial hyperactivity, chronic disease and exacerbation in the absence of treatment. This model uses Brown Norway rats, whose particularity is to produce, like atopic patients, immunoglobulin E (IgE) rates in response to a sensibilization by antigen. The protocol used involves two sensibilizations to ovalbumin at fourteen days interval then a challenge seven days later with ovalbumin aerosol. Forty-eight hours after the antigenic challenge, the animals undergo a bronchoalveolar wash under anesthesia in order to harvest inflammatory cells infiltrate in lung. These cells are then counted and differentiated according to morphological criteria. The products of the invention are administrated by oral route, 1 hour before the antigenic challenge. Most of the preferred compounds of the current invention tested in this model have also demonstrated an excellent activity.

## References

Corrigan and al. (1992) Immunology today 13 : 501-507

Elwood and al. (1995) Inflamm Res 44 : 83-86

## Model of neutrophily in mouse

The studies undertaken from this experimental protocol aim to evaluate modulating effect of the compounds of the invention on the rush of pro-inflammatory cells (precocious phase) in the opening of trachea-bronchial shaft in mouse. This cellular rush is consecutive to stimulation simulating a bacterial infection (bacterial lipopolysaccharid or LPS). This precocious inflammatory step results from events combination among which the main ones are synthesis and release of stimulating (TNF $\alpha$ i) and chimiotactic (IL-8ii) factors, increase of vascular permeability at trachea-bronchial micro-circulation level and neutrophilic polynuclear infiltration which is concomitant to plasmatic protein exudation in pulmonary tissues.

This pathological process is retrieved in chronic obstructive broncho-pneumopathy disease (COPD) in which neutrophils, with macrophage, play a key role in launching of neutrophil recruitment amplification, but also in destructuration of pulmonary tissues (decline of pulmonary functions), hypersecretion of trachea-bronchial mucus (clogging of aerial tracts), tissular inflammation (release of inflammatory mediators and free radicals) and basal tonus increase of pulmonary muscular smooth fibers (chronic respiratory distress). Some of the compounds of the examples have demonstrated an activity in this model.

## References

i SUTER P.M., SUTER S., GIRARDIN E., ROUX-LOMBARD P., GRAU G.E. and DAYER J.-M. 1992. High bronchoalveolar levels of tumor necrosis factor and its inhibitors, interleukin-1, interferon and elastase, in patients with adult respiratory distress syndrome after trauma, shock or sepsis. *Am. Rev. Respir. Dis.* 145: 1016-1022.

ii MARTIN T.R. and GOODMAN R.B. 1999. The role of chemokines in the pathology of the acute respiratory distress syndrome. Chapter 6 in *Chemokines in disease: Biology and clinical research* edited by: C.A. Hébert, Humana Press Inc., Totowa, NJ.

iii REPINE J.E. and BEEHLER C.J. 1991. Neutrophils and the adult respiratory distress syndrome: two interlocking perspectives. *Am. Rev. Respir. Dis.* 144: 251-252.

## **References**

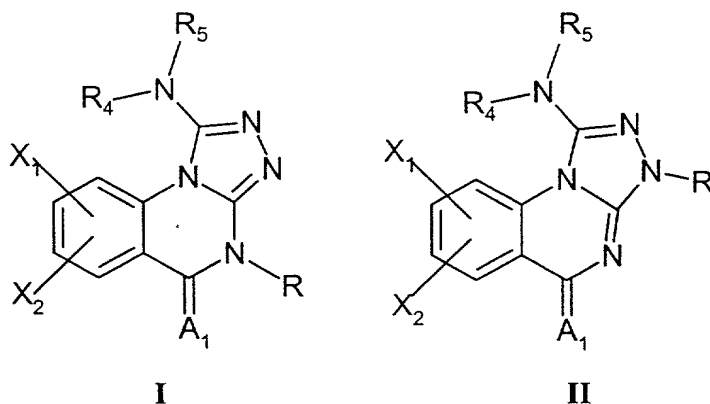
- Barad, M. and al., PNAS, 1998, Vol. 95(25), p. 15020-15025
- Belayev, L. and al., Brain Res., 1998 March 23, Vol. 787(2), p. 277-285
- 5 Block, F. and al., Neuroreport, 1997 December 1, Vol. 8(17), p. 3829-3832
- Egawa, T. and al., J. Pharmacol., 1997 November, Vol. 75(3), p. 275-281
- Goncalves de Moraes, V.-L. and al., Br. J. Pharmacol., 1998 February, Vol. 123(4), p. 631-636
- Hasko, G. and al., Eur. J. Immunol., 1998 February, Vol. 28(2), p. 468-472
- 10 Herzer, W.-A. and al., J. Cardiovasc. Pharmacol., 1998, Vol. 32(5), p. 769-776
- Itoh, A. and al., Methods and Findings in Exp. and Clin. Pharm., 1998, Vol. 20(7), p. 619-625
- Kim, O. H., Lerner A., Blood, 1998 October 1, Vol. 92(7), p. 2484-2494
- Lelkas, Z. and al., Pharmacol. Biochem. Behav., 1998 August, Vol. 60(4), p. 835-839
- Liang, L. and al., Diabetes, 1998 April, Vol. 47(4), p. 570-575
- 15 Merz, K.-H. and al., J. Med. Chem., 1998 November 19, Vol. 41(24), p. 4733-4743
- Miotto, J.-M. and al., Am. J. Respir. Cell. Mol. Biol., 1998 March, Vol. 18(3), p. 411-420



## Claims

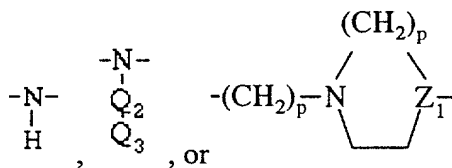
- 5 1. Triazolo [4,3-a] quinazoline-5-ones and/or -5-thiones of formula I or II :

I and II are position isomers of group R on nitrogens 3 or 4, in which :



- $A_1$  is O or S ;
- $X_1$  and  $X_2$ , similar or different, represent :
  - hydrogen, hydroxy, halogen, amino, nitro, mercapto, cyano, carboxy,
  - lower alkyl, lower alkoxy or  $-S(O)_mR_8$  in which m is 0, 1 or 2 and  $R_8$  is a lower alkyl, possibly substituted by one or several halogen atoms,
  - $-CO-Q_1-Q_2-Q_3$  in which :

- $Q_1$ - is : a simple valency bond, -O-,



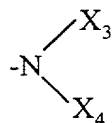
to 3, and  $Z_1$  is CH, N, O or S,

- $Q_2$ - is :

a)  $-(CH_2)_q-$ , q being equal to 0, 1, 2, 3, or 4, or

b)  $-(CH_2-CH_2-O)_r-$ , r being equal to 2, 3, or 4, and

- $Q_3$  is : -H, -OH, lower alkoxy, -O-CO-  $X_3$  -NH $X_3$  or



in which  $X_3$  and  $X_4$ , similar or different, represent one group

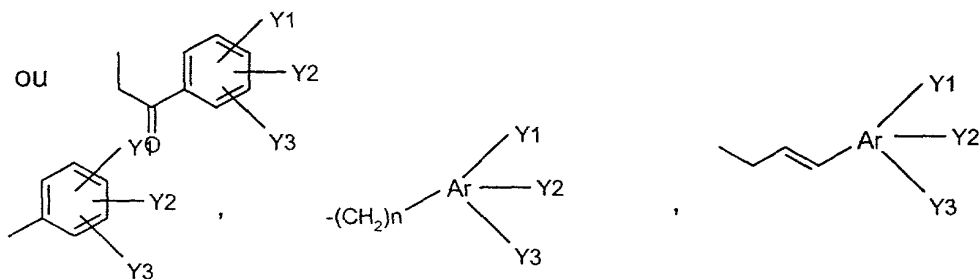
lower alkyl,  $X_3$  and  $X_4$  being able to be linked to form a cycle, including one or several heteroatoms chosen amongst O, S or N,

-  $\text{-NH-R}_1$  in which  $R_1$  represents a lower alkyl group, possibly substituted by one or several groups chosen amongst halogen, hydroxy, cyano, lower alkoxy or  $\text{-CO-Q}_1\text{-Q}_2\text{-Q}_3$ , or

-  $\text{-NR}_2\text{R}_3$  in which  $R_2$  and  $R_3$ , similar or different, represent a lower alkyl, possibly substituted by one or several hydroxy, halogen, cyano, lower alkoxy or  $\text{-CO-Q}_1\text{-Q}_2\text{-Q}_3$  groups,  $R_2$  and  $R_3$  being able to be linked to form a cycle, including one or several heteroatoms chosen amongst O, S or N and possibly bridged by a lower alkyl, gem dialkylated or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, alkoxy or  $\text{-CO-Q}_1\text{-Q}_2\text{-Q}_3$ ;

- R represents :

- lower alkyl, lower alkenyl, lower alkynyl, aryl alkynyl, 2-, 3- or 4-pyridylalkyl



possibly substituted by a lower alkyl, a lower alkoxy, a hydroxy, halogen or amino group,

in which :

- $n$  is an integer between 1 and 5,
- Ar is an aromatic cycle including 5 or 6 atoms with 0 to 3 heteroatoms chosen among O, S or N.
- $Y_1$ ,  $Y_2$  and  $Y_3$ , similar or different represent :
  - hydrogen, hydroxy, mercapto, amino, nitro, halogen,  $\text{-NHR}_1$ ,  $\text{-NHR}_2\text{R}_3$ ,  $\text{(CH}_2\text{)}_5\text{-CN}$ ,  $\text{-(CH}_2\text{)}_s\text{-CO-Q}_1\text{-Q}_2\text{-Q}_3$  in which  $s$  is an integer between 0 to 6 ;

- lower alkyl, lower alkoxy or  $-S(O)_mR_8$  in which m is 0, 1 or 2 and  $R_8$  is a lower alkyl, each one may be possibly substituted by one or several halogen atoms ; and

5

-  $R_4$  and  $R_5$ , represent :

- lower alkyl when  $R_4$  and  $R_5$  are similar, aralkyl, cycloalkyl or cycloalkyl alkyl, when  $R_4$  and  $R_5$  are different,
- lower alkyl,  $R_4$  and  $R_5$  being able to be linked to form a saturated cycle or including one or several double-bonds including one or several heteroatoms chosen among O, S or N and possibly substituted by lower alkyl, hydroxy or lower alkoxy or bridged by a lower alkyl, gem dialkylated or substituted by one or several groups chosen between hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or  $CO-Q_1-Q_2-Q_3$ , two atoms of cycle then formed being also able to be part of another cycle chosen among phenyl or heteroaryl including from 4 to 8 atoms with 1 to 4 heteroatoms ;

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possibly their racemic forms and their isomers, as well as their pharmaceutically acceptable salts.

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2. Triazolo [4,3-a] quinazoline-5-ones and/or -5-thiones according to claim 1, in which :

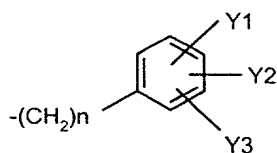
$A_1$  represents an oxygen atom ;

$X_1$  represents a hydrogen and  $X_2$  is a halogen, amino, lower alkyl, hydroxy or  $-NHR_1$  group,  $R_1$  being such as previously defined.

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R represents :

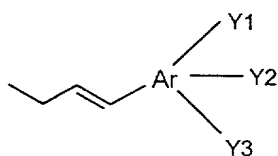
- a lower alkyl, lower alkenyl, aryl alkynyl, 2-, 3- or 4-pyridylalkyl group possibly substituted on a pyridine ring by a lower alkyl, halogen or hydroxy ;



in which :

- n is an integer from 1 to 3,

- Y1, Y2 and Y3 each represent a hydrogen atom or a lower alkoxy group, more particularly methoxy,
- Y1 and Y2 each represent a hydrogen atom and Y3 represents a lower alkoxy group, amino, nitro, hydroxy group,  $-(CH_2)_5CO-Q_1-Q_2-Q_3$  group,  $(CH_2)_5-CN$  group in which,  $Q_1$ ,  $Q_2$ ,  $Q_3$  are such as previously defined, or a lower alkyl possibly substituted by one or several halogen atoms, the particularly preferred of the substituent Y3 being the position 4, or,
- Y1 represents a hydrogen atom and Y2 and Y3, similar or different, represent a hydroxy, halogen or lower alkoxy group, or



in which :

- Ar is such as previously defined ;
- Y1, Y2 and Y3 each represent a hydrogen atom, or
- Y1 and Y2 each represent a hydrogen atom and Y3 is lower alkoxy or halogen ;

$R_4$  and  $R_5$ , represent :

- lower alkyl when  $R_4$  and  $R_5$  are similar, aralkyl, cycloalkyl or cycloalkyl alkyl, when  $R_4$  and  $R_5$  are different,

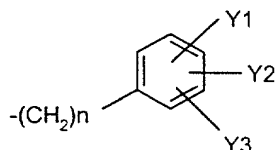
lower alkyl,  $R_4$  and  $R_5$  being able to be linked to form a saturated cycle or including one or several double-bonds with one or several heteroatoms chosen among O, S or N and possibly substituted by a lower alkyl, a hydroxy or a lower alkoxy or bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or  $CO-Q_1-Q_2-Q_3$ , two atoms of the cycle then formed able also to be part of another cycle chosen among phenyl or heteroaryl including from 4 to 8 atoms with 1 to 4 heteroatoms ;

3. Triazolo [4,3-a] quinazoline-5-ones and/or -5-thiones according to claim 1 or 2, in which :

$X_1$  represents a hydrogen atom,

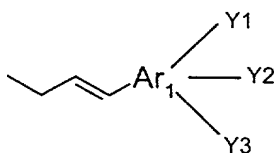
$X_2$  represents a halogen atom, amino, lower alkyl, hydroxy or  $--NHR_1$  ;

5 R represents :



in which :

- n is an integer from 1 to 3,
- $Y_1$ ,  $Y_2$  and  $Y_3$  each represent a hydrogen atom or a lower alkoxy group, more particularly methoxy and in a particular 3, 4, 5-trimethoxy,
- $Y_1$  and  $Y_2$  each represent a hydrogen atom and  $Y_3$  represents a lower alkoxy group, amino, nitro, or hydroxy, a lower alkyl group possibly substituted by one or several halogen atoms, a  $-(CH_2)_sCO-Q_1-Q_2-Q_3$  group in which s is 0 or 1,  $Q_1$  is O,  $-NH-$  or a valency bond,  $Q_2$  is  $-(CH_2)_q-$ , q being equal to 0, 1, 2, 3 or 4 and  $Q_3$  is H, OH or  $-NX_3X_4$  in which  $X_3$  and  $X_4$  are such as previously defined, a  $(CH_2)_s-CN$  group in which s is 0 or 1, the position particularly preferred of the substituent  $Y_3$  being the position 4, or
- $Y_1$  represents a hydrogen atom and  $Y_2$  and  $Y_3$ , similar or different, represent a hydroxy, halogen or lower alkoxy group; or



in which :

- 
- $Ar_1$  is an aromatic cycle including 6 atoms, one may be a nitrogen atom in position 2, 3 or 4 and preferably in position 3 ;
- $Y_1$ ,  $Y_2$  and  $Y_3$  represent each a hydrogen atom, or

- Y1 and Y2 represent each a hydrogen atom and Y3 is a lower alkoxy group or a halogen group when Ar<sub>1</sub> does not include a nitrogen atom; and

R<sub>4</sub> and R<sub>5</sub>, represent :

- lower alkyl when R<sub>4</sub> and R<sub>5</sub> are similar, aralkyl, cycloalkyl or cycloalkyl alkyl, when R<sub>4</sub> and R<sub>5</sub> are different,
- lower alkyl, R<sub>4</sub> and R<sub>5</sub> being able to be linked to form a saturated cycle or including one or several double-bonds with one or several heteroatoms chosen among O, S or N and possibly substituted by a lower alkyl, a hydroxy or a lower alkoxy or bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or CO-Q<sub>1</sub>-Q<sub>2</sub>-Q<sub>3</sub>, two atoms from the cycle then formed able also to be part of another cycle chosen among phenyl or heteroaryl including from 4 to 8 atoms with 1 to 4 heteroatoms ;

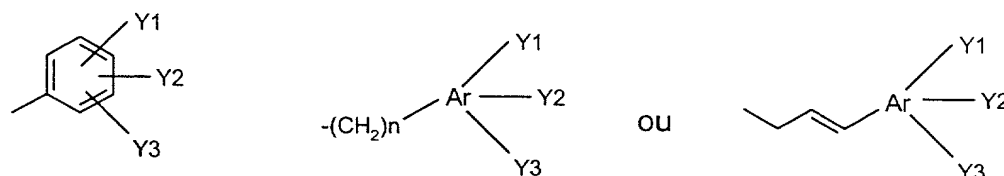
4. Triazolo [4,3-a] quinazoline-5-ones and/or -5-thiones according to any of claims 1 to 3, in which :

- halogen group is chosen among F, Cl, Br or I,
- lower alkyl group is linear or ramified including 1 to 6 carbon atoms,
- lower alkoxy group is linear or ramified including from 1 to 5 carbon atoms,
- lower alkylthio group is linear or ramified including from 1 to 5 carbon atoms,
- lower alkenyl group including from 3 to 6 carbon atoms,
- lower alkynyl group including from 3 to 9 carbon atoms,
- 2-, 3- or 4-pyridylalkyl including an alkyl group with 1 to 5 carbon atoms,
- aryl group including from 5 to 8 atoms,
- aralkyl group including an alkyl group with 1 to 6 carbon atoms,
- cycloalkyl group including 3 to 8 carbon atoms,
- alkyl cycloalkyl group including an alkyl with 1 to 6 carbon atoms
- lower alkyl, lower alkoxy or lower alkylthio substituted by one or several halogen atoms which are chosen among the groups -(CH<sub>2</sub>)<sub>p</sub>-CF<sub>3</sub>, -O-(CH<sub>2</sub>)<sub>p</sub>-CF<sub>3</sub> or -S-(CH<sub>2</sub>)<sub>p</sub>-CF<sub>3</sub>, in which p is an integer from 0 to 3.

5. Triazolo [4,3-a] quinazoline-5-ones and/or -5-thiones according to claim 1, in which :

- $A_1$  is O or S ;
- $X_1$  and  $X_2$ , similar or different, represent :
  - hydrogen, hydroxy, halogen, amino, nitro, mercapto, cyano, carboxy,
  - lower alkyl, lower alkoxy or  $-S(O)_mR_8$  in which m is 0, 1 or 2 and  $R_8$  is lower alkyl,

- R represents:



in which :

- n is an integer from 1 to 5,
- Ar is an aromatic cycle including 5 or 6 atoms with 0 to 3 heteroatoms chosen among O, S or N,
- $Y_1$ ,  $Y_2$  and  $Y_3$ , similar or different represent :
  - hydrogen, hydroxy, mercapto, amino, nitro, halogen,  $-(CH_2)_sCO-Q_1-Q_2-Q_3$ ,  $(CH_2)_s-CN$  in which s is an integer from 0 to 6 ;
  - lower alkyl, lower alkoxy or  $-S(O)_mR_8$  in which m is 0, 1 or 2 and  $R_8$  is a lower alkyl, possibly substituted by one or several halogen atoms.

- $R_4$  and  $R_5$ , similar or different, represent :
  - lower alkyl,  $R_4$  and  $R_5$  being able to be linked to form a saturated cycle or including one or several double-bonds with one or several heteroatoms chosen among O, S or N and possibly bridged by a lower alkyl, dialkylated gem or substituted by one or several groups chosen among hydroxy, keto, lower alkyl, lower alkoxy, phenyl alkyl or  $CO-Q_1-Q_2-Q_3$ .

6. Triazolo [4,3-a] quinazoline-5-ones and/or -5-thiones according to claim 5, chosen among the group including :

7-Bromo-1-dimethylamino-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(3,4-Dimethoxy-benzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Methyl-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Azepan-1-yl-7-methyl-4-pyridin-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

Dimethylamino-methyl-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7. Triazolo [4,3-a] quinazoline-5-ones and/or -5-thiones according to claim 1, 2, 3, or 4, chosen among the group including :

1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-pyridin-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-pyridin-3-ylmethyl-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-allyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one



1-(azepan-1-yl)-7-chloro-4-(4-methylbenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(2-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(3-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(4-bromobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(4-(trifluoromethyl)benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(4-cyanobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(2-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(3-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(4-methoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(3,4-dichlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(2-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(4-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(2-phenylethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)ethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(3-phenylpropyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-chloro-4-(2-oxo-2-phenyl-ethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-[2-(4-methoxyphenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-[2-(4-chlorophenyl)-2-oxoethyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

5-[(1-(azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]-quinazolin-4-yl)acetyl]-2-methoxybenzoic acid methyl ester

7-Chloro-4-pyridin-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-bromo-4-(4-chlorophenylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-(4-fluoro-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-bromo-4-(3-pyridinylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-[3-(4-chloro-phenyl)-allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-[3-(4-methoxy-phenyl)-allyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methyl-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-chloro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-fluoro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

3-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester

7-Bromo-4-(4-nitro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl ester

7-Bromo-4-(4-hydroxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,4-dimethoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzo[1,3]dioxol-5-ylmethyl-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,5-dimethoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-pyrrolidin-1-yl-4-(3,4,5-trimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-[(E)-3-(4-chloro-phenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-[3-(4-methoxy-phenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-((E)-3-pyridin-4-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,5-dimethyl-isoxazol-4-ylmethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-cyclopentylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-butyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-pyrrolidin-1-yl-4-(2,2,2-trifluoro-ethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(2-hydroxy-ethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(2-diethylamino-ethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-prop-2-ynyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(2-phenoxy-ethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(2-phenylsulfényl-ethyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)-phenyl-acetic acid methyl ester

4-(7-Bromo-5-oxo-1-piperidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Bromo-4-(3,4-dimethoxy-benzyl)-1-piperidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(piperidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3-pyridin-3-yl-allyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(4-methyl-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Bromo-1-dimethylamino-4-(4-hydroxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester

[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetonitrile

7-Bromo-1-dimethylamino-4-(pyridin-3-ylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-prop-2-ynyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-yl)-phenyl-acetic acid methyl ester

1-Azepan-1-yl-7-methyl-4-pyridin-3-ylmethyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-methyl-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-(3,4-Dimethoxy-benzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester

[4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

7-Methyl-4-pyridin-3-ylmethyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Methyl-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Methyl-5-oxo-1-thiomorpholin-4-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

7-Methyl-4-(3-pyridin-3-yl-allyl)-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Dimethylamino-7-methyl-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

[4-(Dimethylamino-methyl-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

1-Dimethylamino-7-methyl-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Dimethylamino-7-methyl-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-8-methyl-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

(4-Cyano-benzyl)-dimethylamino-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

7-Hydroxy-4-((E)-3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

3-Allyl-1-azepan-1-yl-7-chloro-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-benzyl-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-Azepan-1-yl-7-chloro-3-(4-methyl-benzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(2-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(3-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(4-bromobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(4-(trifluoromethyl)benzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(4-cyanobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(2-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(3-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(4-methoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(3,4-dichlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(2-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(3-pyridylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(2-phenylethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)ethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-(3-phenylpropyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-chloro-3-(2-oxo-2-phenyl-ethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-[2-(4-methoxyphenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-3-[2-(4-chlorophenyl)-2-oxoethyl]-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

5-[(1-(azepan-1-yl)-7-chloro-5-oxo-5H-[1,2,4]triazolo[4,3-a]-quinazolin-3-yl)acetyl]-2-methoxybenzoic acid methyl ester

1-(azepan-1-yl)-7-bromo-3-(4-chlorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-bromo-3-(4-fluorobenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-(azepan-1-yl)-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]-quinazolin-3-ylmethyl)-benzonitrile

1-(azepan-1-yl)-7-bromo-3-(3,4-dimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Bromo-5-oxo-1-perhydro-azepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-phenyl]-acetic acid

1-(azepan-1-yl)-7-bromo-3-(pyridin-3-ylmethyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-3-((E)-3-phenyl-allyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-((E)-3-phenyl-allyl)-1-piperidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-bromo-3-(4-chlorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-bromo-3-(4-fluorobenzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one



4-(7-bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]-quinazolin-3-ylmethyl)-benzonitrile

4-(7-bromo-5-oxo-1-(pyrrolidin-1-yl)-5H-[1,2,4]triazolo[4,3-a]-quinazolin-3-ylmethyl)benzoic acid methyl ester

7-Bromo-3-(4-methoxy-benzyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-phenyl ester

7-Bromo-1-dimethylamino-3-(4-hydroxy-benzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

3-(benzo[1,3]dioxol-5-ylmethyl)-7-bromo-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-bromo-3-(3,5-dimethoxy-benzyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo- [4,3-a]quinazolin-5-one

7-bromo-1-(pyrrolidin-1-yl)-3-(3,4,5-trimethoxybenzyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-3-(1H-imidazol-4-ylmethyl)-1-pyrrolidin-1-yl-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-bromo-3-(n-butyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)-phenyl-acetic acid methyl ester

7-Bromo-1-dimethylamino-3-(3-phenyl-allyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-yl)-phenyl-acetic acid methyl ester

1-(azepan-1-yl)-7-methyl-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-methyl-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-3,8-dimethyl-3H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-Azepan-1-yl-8-methyl-3-((E)-3-phenyl-allyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-hydroxy-3-(3-phenylallyl)-1-(pyrrolidin-1-yl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1,8-bis(azepan-1-yl)-3-(3-phenylallyl)-3H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-4-benzyl-7-bromo-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

4-Benzyl-7-bromo-1-(butyl-methyl-amino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-benzyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-chloro-1-dibutylamino-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-chloro-4-methyl-1-(piperidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-Chloro-4-methyl-1-(4-methyl-piperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Chloro-4-methyl-1-(1,8,8-trimethyl-3-aza-bicyclo[3.2.1]oct-3-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-phenyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

4-benzyl-7-chloro-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

4-benzyl-7-chloro-1-(piperidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(azepan-1-yl)-8-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(azepan-1-yl)-4-benzyl-8-chloro-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(azepan-1-yl)-7-bromo-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

4-benzyl-7-bromo-1-(piperidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

4-Benzyl-7-bromo-1-dimethylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-morpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(4-methyl-piperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(4-phenyl-piperazin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-(4-benzyl-piperazin-1-yl)-7-bromo-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(3,6-dihydro-2H-pyridin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(2,5-dihydro-pyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-(3-hydroxy-pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-methylamino-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-dimethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methyl-1-thiomorpholin-4-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-benzyl-8-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-benzyl-7-methoxy-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methoxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

1-Azepan-1-yl-4-benzyl-7-nitro-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-4-benzyl-7-chloro-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(azepan-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-6-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-ethyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-chloro-4-methyl-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-chloro-4-methyl-1-(morpholin-4-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(azocan-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

7-chloro-1-(3,4-dihydro-2H-quinolin-1-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(4-benzylpiperidin-1-yl)-7-chloro-4-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-chloro-4-methyl-1-(1,3,3-trimethyl-6-azabicyclo[3,2,1]oct-6-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(azepan-1-yl)-7-fluoro-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(azepan-1-yl)-7-iodo-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

1-(azepan-1-yl)-7-methoxy-4-methyl-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

4-Benzyl-7-bromo-1-(ethyl-methyl-amino)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-diethylamino-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-bromo-1-pyrrol-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(4-Amino-benzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-hydroxy-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Hydroxy-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl)-acetamide

N-[5-Oxo-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl]-acetamide

7-Amino-4-((E)-3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-benzyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Amino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Amino-4-((E)-3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(Amino-dimethylamino-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Amino-1-dimethylamino-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

N-(4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-7-yl)-methanesulfonamide

4-Benzyl-7-dimethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-1-dimethylamino-5-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carbonitrile

4-Benzyl-5-oxo-1-pyrrolidin-1-yl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carboxylic acid

[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid methyl ester

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methyl-acetamide

2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethyl-acetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-hydroxy-acetamide

4-(1-Dimethylamino-7-methyl-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-(7-Bromo-1-dimethylamino-5-thioxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

4-benzyl-7-(N,N-dimethylsulfonylamino)-1-(pyrrolidin-1-yl)-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-one

8. Triazolo [4,3-a] quinazoline-5-ones and/or -5-thiones according to anyone of claim 1 to 4, chosen among the groups including :

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1-(Azepan-1-yl)-7-chloro-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(4-chlorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(4-fluorobenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-bromo-4-(4-chlorophenylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methyl-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-chloro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-fluoro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester

7-Bromo-4-(4-nitro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

Acetic acid 4-(7-bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl ester

7-Bromo-4-(4-hydroxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,4-dimethoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-[(E)-3-(4-chloro-phenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-[3-(4-methoxy-phenyl)-allyl]-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-((E)-3-pyridin-4-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,4-dimethoxy-benzyl)-1-piperidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(piperidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one



7-Bromo-1-dimethylamino-4-(4-methyl-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

7-Bromo-1-dimethylamino-4-(4-hydroxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(Bromo-dimethylamino-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester

[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetonitrile

7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-methyl-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(3,4-Dimethoxy-benzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Methyl-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

7-Methyl-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(Dimethylamino-methyl-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid

1-Dimethylamino-7-methyl-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Bromo-5-oxo-1-perhydro-azepin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-3-ylmethyl)-phenyl]-acetic acid

4-benzyl-7-bromo-1-(pyrrolidin-1-yl)-4H-[1,2,4]triazolo[4,3-a]-quinazolin-5-one

4-Benzyl-7-bromo-1-(2,5-dihydro-pyrrol-1-yl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-iodo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-4-benzyl-7-methyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(4-Amino-benzyl)-7-bromo-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-((E)-3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-1-azepan-1-yl-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-((E)-3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-1-dimethylamino-4-((E)-3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-Benzyl-8-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-ethylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-isopropylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid methyl ester

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methyl-acetamide

2-[4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethyl-acetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-hydroxy-acetamide

1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

9. Triazolo [4,3-a] quinazoline-5-ones and/or -5-thiones according to any of claims 1 to 4, chosen among the group including :

Bromo-dimethylamino-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(3,4-dimethoxybenzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-chloro-4-(3-pyridylmethyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(1-Azepan-1-yl-7-bromo-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

1-Azepan-1-yl-7-bromo-4-(3,4-dimethoxy-benzyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(azepan-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-((E)-3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-bromo-4-(3-pyridin-4-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-methyl-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(4-chloro-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3,4-dimethoxy-benzyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(pyrrolidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-4-(3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-(piperidin-1-yl)-7-bromo-4-(3-phenylallyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Bromo-1-dimethylamino-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

4-(Bromo-dimethylamino-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzoic acid methyl ester

7-Bromo-1-dimethylamino-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Bromo-1-dimethylamino-4-(3-phenyl-prop-2-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

1-Azepan-1-yl-7-methyl-4-(3-phenyl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(3,4-Dimethoxy-benzyl)-7-methyl-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Methyl-4-(3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-((E)-3-phenyl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

7-Amino-4-((E)-3-pyridin-3-yl-allyl)-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-Benzyl-7-methylamino-1-pyrrolidin-1-yl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one

4-(7-Methylamino-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-benzonitrile

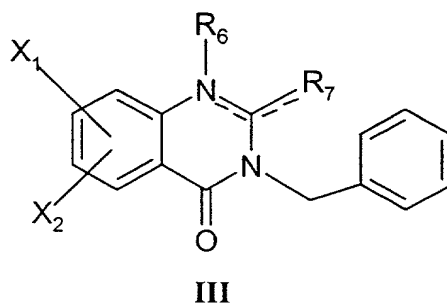
[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-acetic acid methyl ester

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N-methyl-acetamide

2-[4-(7-Bromo-5-oxo-1-pyrrolidin-1-yl-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl)-phenyl]-N,N-dimethyl-acetamide

1-Dimethylamino-7-methyl-4-(3-pyridin-3-yl-allyl)-4H-[1,2,4]triazolo[4,3-a]quinazoline-5-thione

10. Intermediates compounds of general formula III :

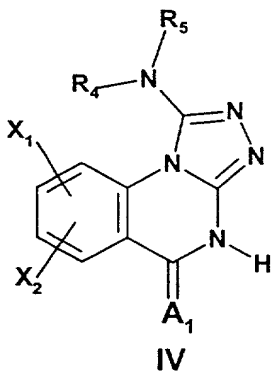


in which :

- $X_1$ ,  $X_2$  and  $A_1$  are such as defined in claim 1 ;
- dotted lines represent optional double-bound ;
- $R_6$  is hydrogen ; and
- $R_7$  is S or hydrazino ;

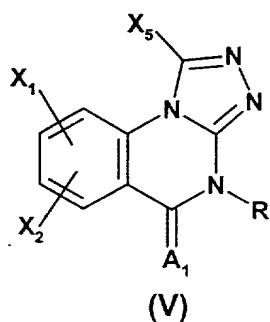
$R_7$  being able to be linked to nitrogen in  $R_6$  to form a cycle, particularly a triazole, possibly substituted by lower thioalkyl group, mercapto or halogen.

**11. Intermediates compounds of general formula IV :**



in which  $X_1$ ,  $X_2$ ,  $A_1$ ,  $R_4$  and  $R_5$  are such as defined in claim 1.

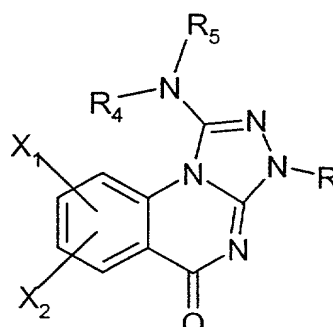
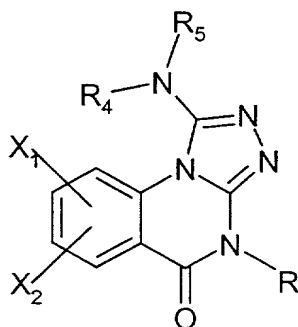
**12. Intermediates compounds of general formula V :**



in which  $X_1$ ,  $X_2$ ,  $A_1$  and  $R$  are such as previously defined in claim 1 and  $X_5$  is a halogen group, particularly  $F$ ,  $Br$  or  $Cl$ ,  $-OCOX_7$ ,  $-OSO_2X_7$  or  $-SO_2X_7$  in which  $X_7$  is a lower alkyl or aryl group.

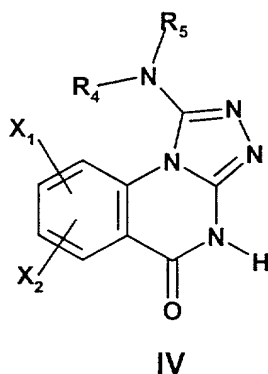
5

13. A process for producing compounds of general formula I and II :



in which  $X_1$ ,  $X_2$ ,  $R$ ,  $R_4$  and  $R_5$  are such as previously defined in claim 1,

said process being characterized in that it includes reacting a general formula IV compound :



10

in which  $X_1$ ,  $X_2$ ,  $R_4$  and  $R_5$  are such as previously defined in claim 1,

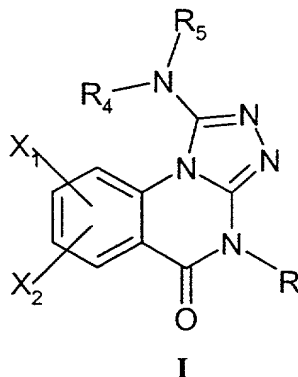
with a compound of general formula



in which R is such as previously defined and X' is a halogen group, particularly F, Br or Cl, -OCOX<sub>7</sub> or -OSO<sub>2</sub>X<sub>7</sub> in which X<sub>7</sub> is a lower alkyl or aryl group;

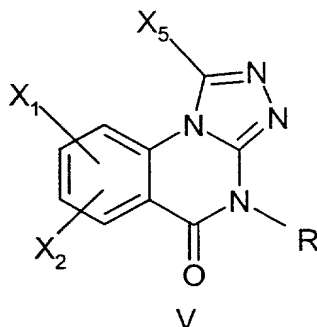
5 to obtain a mixture of general formula I and II compounds which are then possibly separated.

14. A process for producing general formula I compounds:



in which X<sub>1</sub>, X<sub>2</sub>, R, R<sub>4</sub> and R<sub>5</sub> are such as defined in claim 1,

said process being characterized in that it includes reacting a general formula V compound :



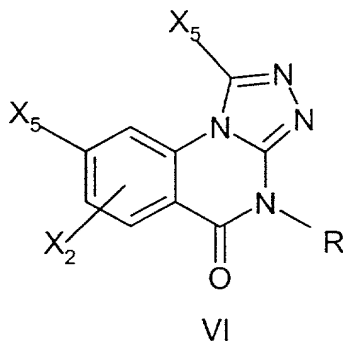
10

in which X<sub>1</sub>, X<sub>2</sub> and R are such as defined in claim 1 and X<sub>5</sub> is a halogen group, particularly F, Br or Cl, -OCOX<sub>7</sub>, -OSO<sub>2</sub>X<sub>7</sub> or -SO<sub>2</sub>X<sub>7</sub> in which X<sub>7</sub> is a lower alkyl or aryl group;  
with a general formula compound :



15 in which R<sub>4</sub> and R<sub>5</sub> are such as defined in claim 1,  
to obtain a compound of general formula I.

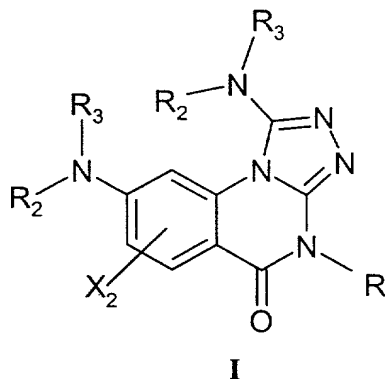
15. Process according to claim 14, characterized in that when  $X_1$  is  $-NR_2R_3$  and  $-NR_2R_3$  and  $-NR_4R_5$  are identical, formula I compounds are obtained by reacting a compound of general formula VI :



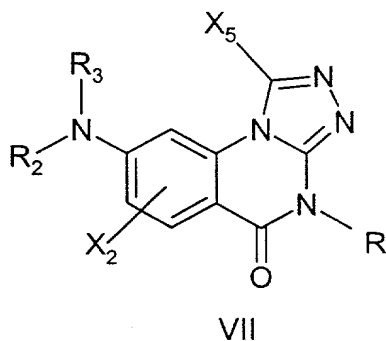
in which  $X_2$ ,  $X_5$  and R are such as defined in claim 20,  
with a compound of general formula :



in which  $R_2$  and  $R_3$  are such as defined in claim 20,  
to obtain a compound of general formula (I) :



16. Process according to claim 14, characterized in that when  $X_1$  is  $-NR_2R_3$  and  $-NR_2R_3$  and  $-NR_4R_5$  are different, formula I compounds are obtained by reacting a compound of general formula VII :

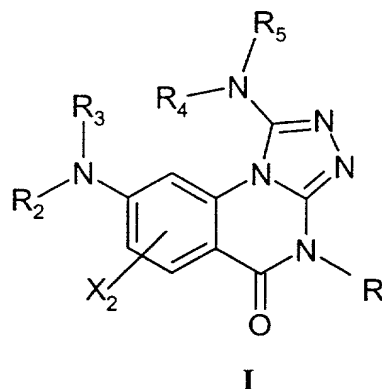




in which  $X_2$ ,  $X_5$ , R,  $R_2$  and  $R_3$  are such as defined in claim 20  
with a compound of general formula :



- 5 in which  $R_4$  and  $R_5$  are such as defined in claim 20,  
to obtain a compound of general formula (I) :



17. Pharmaceutical composition including a compound according to any of claims 1 to 9 and  
a pharmacologically acceptable carrier.

18. Use of a compound according to any of claims 1 to 9 for drug preparation intended for  
treatment of disease or illness relying on therapy by phosphodiesterase inhibition, and  
more particularly of PDE4.

19. Use according to claim 18, characterized in that the disease is asthma.

20. Use according to claim 18, characterized in that the disease is chronic bronchitis or acute  
pulmonary attack.

21. Use according to claim 18, characterized in that the disease is atopic dermatitis.

22. Use according to claim 18, characterized in that the disease is pulmonary high blood  
pressure.

23. Use according to claim 18, characterized in that the disease is cardiac or pulmonary  
insufficiencies.

24. Use according to claim 18, characterized in that the disease is psoriasis.

25. Use according to claim 18, characterized in that the disease is inflammatory disease of  
digestive system such as hemorrhagic rectocolitis or Crohn's disease.

26. Use according to claim 18, characterized in that the disease is diabetes or a disease linked  
to high TNF- $\alpha$  levels such as acute respiratory distress syndrome and acute pancreatitis.

27. Use according to claim 18, characterized in that the disease is benign prostate  
hypertrophy.

28. Use according to claim 18, characterized in that the disease is chosen among rheumatoid  
arthritis and multiple sclerosis.

29. Use according to claim 18, characterized in that the disease is chosen among depression,  
neuronal attack caused by ischemia and partial cerebral ischemia.

30. Use according to claim 18, characterized in that the disease is cancer, more particularly  
malignant tumors or chronic lymphoid leukemia.

31. Use of a compound according to any of claims 1 to 9 to attenuate development of  
tolerance phenomena or morphine dependence.

32. Use of a compound according to any of claims 1 to 9 to decrease losses of behavioral  
memory.

33. Use of a compound according to any of claims 1 to 9 to prevent premature child birth.

34. Use according to claim 18, characterized in that the disease is septicemia or polyvisceral  
deficiencies.

**Declaration and Power of Attorney for Patent Application****Déclaration et Pouvoirs pour Demande de Brevet****French Language Declaration**

En tant que l'inventeur nommé ci-après, je déclare par le présent acte que:

mon domicile, mon adresse postale et ma nationalité sont ceux énoncés ci-dessous à côté de mon nom.

Je crois être le premier inventeur original et unique (si un seul nom est mentionné ci-dessous), ou l'un des premiers inventeurs originaux (si plusieurs noms sont mentionnés ci-dessous) de l'objet revendiqué, pour lequel une demande de brevet a été déposée concernant l'invention intitulée

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

1-AMINO TRIAZOLO[4,3-a]QUINAZOLINE-5-ONES AND/OR  
-5-THIONES INHIBITING PHOSPHODIESTERASE IV

NOUVELLES 1-AMINO TRIAZOLO[4,3-a]QUINAZOLINE-5-ONES ET/OU -5-THIONES INHIBITRICES DE PHOSPHODIESTERASES IV

et dont la description est fournie ci-joint à moins que la case suivante n'ait été cochée:

the specification of which is attached hereto unless the following box is checked:

☒ a été déposée le 28 avril 2000  
sous le numéro de demande des Etats-Unis ou le numéro de demande international PCT  
PCT/FR00/01174 et modifiée le  
(le cas échéant).

☒ was filed on 28 April 2000  
as United States Application Number or PCT  
International Application PCT/FR00/01174  
and was amended on  
(if applicable).

Je déclare par le présent acte avoir passé en revue et compris le contenu de la description ci-dessus, revendications comprises, telles que modifiées par toute modification dont il aura été fait référence ci-dessus.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

Je reconnais devoir divulguer toute information pertinente à la brevetabilité, comme défini dans le Titre 37, § 1.56 du Code fédéral des réglementations.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## French Language Declaration

Je revendique par le présent acte avoir la priorité étrangère, en vertu du Titre 35, § 119(a)-(d) ou § 365(b) du Code des Etats-Unis, sur toute demande étrangère de brevet ou certificat d'inventeur ou, en vertu du Titre 35, § 365(a) du même Code, sur toute demande internationale PCT désignant au moins un pays autre que les Etats-Unis et figurant ci-dessous et, en cochant la case, j'ai aussi indiqué ci-dessous toute demande étrangère de brevet, tout certificat d'inventeur ou toute demande internationale PCT ayant une date de dépôt précédant celle de la demande à propos de laquelle une priorité est revendiquée.

Prior foreign application(s)  
Demande(s) de brevet antérieure(s)

99/05398

(Number)

(Numéro)

France

(Country)

(Pays)

28 April 1999

(Day/Month/Year Filed)

(Jour/Mois/Année de dépôt)

Priority Not Claimed  
Droit de priorité revendiqué



(Number)

(Numéro)

(Country)

(Pays)

(Day/Month/Year Filed)

(Jour/Mois/Année de dépôt)



Je revendique par le présent acte tout bénéfice, en vertu du Titre 35, § 119(e) du Code des Etats-Unis, de toute demande de brevet provisoire effectuée aux Etats-Unis et figurant ci-dessous.

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application No.)

(N° de demande)

(Filing Date)

(Date de dépôt)

(Application No.)

(N° de demande)

(Filing Date)

(Date de dépôt)

Je revendique par le présent acte tout bénéfice, en vertu du Titre 35, § 120 du Code des Etats-Unis, de toute demande de brevet effectuée aux Etats-Unis, ou en vertu du Titre 35, § 365(c) du même Code, de toute demande internationale PCT désignant les Etats-Unis et figurant ci-dessous et, dans la mesure où l'objet de chacune des revendications de cette demande de brevet n'est pas divulgué dans la demande antérieure américaine ou internationale PCT, en vertu des dispositions du premier paragraphe du Titre 35, § 112 du Code des Etats-Unis, je reconnais devoir divulguer toute information pertinente à la brevetabilité, comme défini dans le Titre 37, § 1.56 du Code fédéral des réglementations, dont j'ai pu disposer entre la date de dépôt de la demande antérieure et la date de dépôt de la demande nationale ou internationale PCT de la présente demande:

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

PCT/FR00/01174

(Application No.)

(N° de demande)

28 April 2000

(Filing Date)

(Date de dépôt)

Pending

(Status) (patented, pending, abandoned)

(Statut) (breveté, en cours d'examen, abandonné)

(Application No.)

(N° de demande)

(Filing Date)

(Date de dépôt)

(Status) (patented, pending, abandoned)

(Statut) (breveté, en cours d'examen, abandonné)

Je déclare par le présent acte que toute déclaration ci-incluse est, à ma connaissance, véridique et que toute déclaration formulée à partir de renseignements ou de suppositions est tenue pour véridique; et de plus, que toutes ces déclarations ont été formulées en sachant que toute fausse déclaration volontaire ou son équivalent est passible d'une amende ou d'une incarcération, ou des deux, en vertu de la Section 1001 du Titre 18 du Code des Etats-Unis, et que de telles déclarations volontairement fausses risquent de compromettre la validité de la demande de brevet ou du brevet délivré à partir de celle-ci.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

PTO/SB/105 (2-98)

Approved for use through 9/30/98. OMB 0851-0032

Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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**French Language Declaration**

**POUVOIRS:** En tant que l'inventeur cité, je désigne par la présente l'(les) avocat(s) et/ou agent(s) suivant(s) pour qu'ils poursuive(nt) la procédure de cette demande de brevet et traite(nt) toute affaire s'y rapportant avec l'Office des brevets et des marques: (mentionner le nom et le numéro d'enregistrement).

Adresser toute correspondance à:

Charles W. Ashbrook (Reg. No. 27,610)  
 Heidi M. Berven (Reg. No. P-48,951)  
 Evan J. Federman (Reg. No. 37,060)  
 Mehdi Ganjeizadeh (Reg. No. 47,585)  
 Rosanne Goodman (Reg. No. 32,534)  
 Suzanne M. Harvey (Reg. No. 42,640)  
 David R. Kurlandsky (Reg. No. 41,505)

**POWER OF ATTORNEY:** As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: (list name and registration number).

Send Correspondence to:

Darryl C. Little (Reg. No. 40,703)  
 J. Trevor Lumb (Reg. No. 28,567)  
 James Proscia (Reg. No. 47,010)  
 Claude F. Purchase, Jr. (Reg. No. 47,871)  
 Francis J. Tinney (Reg. No. 33,069)  
 Linda A. Vag (Reg. No. 32,071)

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Claude F. Purchase, Jr.  
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Direct Telephone Calls to: (name and telephone number)

Claude F. Purchase, Jr.  
 (734) 622-1692

Nom complet de l'unique ou premier inventeur GAUDILLIERE, Bernard	Full name of sole or first inventor GAUDILLIERE, Bernard
Signature de l'inventeur Date	Inventor's signature Date <u>22.10.01</u>
Domicile 92000 Nanterre, France	Residence 92000 Nanterre, France <u>FR V</u>
Nationalité France	Citizenship France
Adresse postale 28, rue de Zillina 92000 Nanterre France	Post Office Address 28, rue de Zillina 92000 Nanterre France
Nom complet du second co-inventeur, le cas échéant LAVALETTE, Remi	Full name of second joint inventor, if any LAVALETTE, Remi
Signature du second inventeur Date	Second Inventor's signature Date <u>22/10/01</u>
Domicile 91160 Longjumeau, France	Residence 91160 Longjumeau, France <u>FR V</u>
Nationalité France	Citizenship France
Adresse postale 5, rue Leontine Sohler 91160 Longjumeau France	Post Office Address 5, rue Leontine Sohler 91160 Longjumeau France

(Fournir les mêmes renseignements et la signature de tout co-inventeur supplémentaire.)

(Supply similar information and signature for third and subsequent joint inventors.)

**French Language Declaration**

**POUVOIRS:** En tant que l'inventeur cité, je désigne par la présente l'(les) avocat(s) et/ou agent(s) suivant(s) pour qu'ils poursuive(nt) la procédure de cette demande de brevet et traite(nt) toute affaire s'y rapportant avec l'Office des brevets et des marques: (mentionner le nom et le numéro d'enregistrement).

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 David R. Kurlandsky (Reg. No. 41,505)

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 J. Trevor Lamb (Reg. No. 28,567)  
 James Proscia (Reg. No. 47,010)  
 Claude F. Purchase, Jr. (Reg. No. 47,871)  
 Francis J. Tinney (Reg. No. 33,069)  
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Nom complet du <del>third</del> co-inventeur, le cas échéant ANDRIANJARA, Charles	Full name of <del>third</del> joint inventor, if any ANDRIANJARA, Charles
Signature de l'inventeur Date	Inventor's signature Date
Domicile 94260 Fresnes, France	Residence 94260 Fresnes, France FRX
Nationalité France	Citizenship France
Adresse postale 3, rue Auguste Daix 94260 Fresnes France	Post Office Address 3, rue Auguste Daix 94260 Fresnes France
Nom complet du <del>fourth</del> co-inventeur, le cas échéant BREUZARD, Francine	Full name of <del>fourth</del> joint inventor, if any BREUZARD, Francine
Signature du second inventeur Date	Second Inventor's signature Date
Domicile 91400 Quincy sous Senart, France	Residence 91400 Quincy sous Senart, France FRX
Nationalité France	Citizenship France
Adresse postale 42, rue Fontaine Cornaille 91400 Quincy sous Senart France	Post Office Address 42, rue Fontaine Cornaille 91400 Quincy sous Senart France

(Fournir les mêmes renseignements et la signature de tout co-inventeur supplémentaire.)

(Supply similar information and signature for third and subsequent joint inventors.)